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PNEUMONIA DUE TO PNEUMOCOCCUS TYPE VII (COOPER)

SPECIFIC SERUM TREATMENT

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In our series Pneumococcus type VII (Cooper) was responsible for 6.5 per cent of the cases of pneumococcic pneumonia in adults and for 2.4 per cent of the cases of pneumococcic pneumonia in children.

During the seven years from 1928 to 1935 there were observed in the wards of the Harlem Hospital 218 patients with pneumonia due to Pneumococcus type VII. Of these, 200 were adults and 18 were children. The number of cases and the relative incidence of this type of pneumonia varied from year to year. In the series for adults in the years 1929-1930 and 1930-1931 the cases of pneumonia due to Pneumococcus type VII were relatively most numerous, 37 cases (9 per cent). In the year 1934-1935 this type occurred in 24 cases, only 4.6 per cent of the total number of cases of pneumonia for that year.[1]

Of the adult patients with type VII pneumonia, 157 (78.5 per cent) were men and 43 (21.5 per cent) were women. The predominance in men occurred in all decades except the eighth.

This study received financial support in part from the Metropolitan Life Insurance Company.

The cases reported here include those previously reported by one of us (J. G. M. B.) in connection with the use of therapeutic serum.

From the Littauer Pneumonia Research Fund of the New York University, College of Medicine; from the Medical Service, Harlem Hospital (Department of Hospitals), and from the Research Laboratories (Department of Health).

1. In the year 1935-1936 there were 85 cases (13.3 per cent) of type VII pneumonia.

MODE OF ONSET AND COURSE

In only 40 (20.6 per cent) of 194 adults was the onset preceded by a cold in the head or in the chest. In 152 cases (78.4 per cent) the illness started with a chill and in 175 cases (90.2 per cent) with pain in the chest (6 cases were omitted because the histories were unobtainable).

The graphs of the temperature of the 41 patients who were not given serum and who came to the hospital on the third day of the disease or earlier may be divided as follows: Twenty-three curves (56.1 per cent) showed a constantly elevated temperature of a single phase; 10 (24.4 per cent) were biphasic, that is, there was a drop in temperature of more than 3 F. which lasted twenty-four hours or longer, and 8 (19.5 per cent) were polyphasic, having several such drops in temperature. The polyphasic temperature curves were typical of sepsis, displaying marked fluctuations of less than twenty-four hours' duration. Four patients did not show a rise in temperature above 102 F., yet 1 of these patients died. The 11 patients whose pulse rate was always below 110 survived.

SEVERITY

Type VII pneumonia is moderately severe. Twenty-eight (18.8 per cent) of the 149 adult patients who were not given serum died. The mortality was slightly higher among the men. Twenty-three (19.7 per cent) of the 117 men died, whereas only 5 (15.6 per cent) of the 32 women died.

The mortality among infants was highest. Two of 5 children under 2 years of age who did not receive serum died. All 10 children from 2 to 12 years of age and the 9 patients in the 12 to 20 year period survived. After the age of 50 the mortality was as high as among infants. Seventeen of the 104 men under 50 died, a mortality of 16.3 per cent, and 5 of the 12 men over 50 died, a mortality of 41.6 per cent. The death of one male was omitted from this series because his age was unknown. Three of the 29 women under 50 died, a mortality of 10.3 per cent, and 2 of the 3 women over 50 died, a mortality of 66.7 per cent.

The occurrence of high fever, rapid pulse rate or some menacing symptom, such as delirium, severe anoxia, distention, dehydration, pulmonary edema or a rating of less than 50 (in accordance with our method of rating given elsewhere[2]), characterized the cases of severe pneumonia. Cases of moderately severe pneumonia were those in which the rating was always between 50 and 70, and cases of mild pneumonia were those in which the rating never was below 75. In the series of adults, after excluding the 6 fatal cases in which there was an associated

2. Bullowa, J. G. M.: Use of Antipneumococcic Refined Serum in Lobar Pneumonia, J. A. M. A. **90**:1349 (April 28) 1928.

lethal condition, pneumonia was severe in 73 (37.6 per cent) of the 194 cases, moderate in 86 (44.3 per cent) and mild in 35 (18 per cent).

Death occurred in 47.4 per cent of those who were irritable, 48.3 per cent of those who were delirious, 85.7 per cent of those who had pulmonary edema and 47.6 per cent of those who were dehydrated. The 2 patients who hiccupped died. The influence of these and additional factors are shown in table 1.

TABLE 1.—*Occurrence of Symptoms and Effect on Outcome Among Two Hundred Adult Patients with Type VII Pneumonia* *

	All Cases in Which There Were Symptoms	Percentage of Total (200) Cases	Fatal Cases in Which There Were Symptoms	Percentage of Fatal Cases (33) in Which Symptoms Occurred	Fatality in Cases in Which Symptoms Occurred, Percentage
Onset:					
Preceded by cold in head or chest..	40	20.6	5	16.1	12.5
Chill at onset.....	152	78.4	23	74.2	15.1
Pain in chest.....	175	90.2	26	83.9	14.9
Course:					
Temperature always below 102 F...	4	2.0	1	3.0	25.0
Pulse rate always below 110.....	11	5.5	0	0.0	0.0
Symptoms:					
Cyanosis.....	109	54.5	22	66.7	20.2
Anoxemia (requiring oxygen).....	88	44.0	22	66.7	25.0
Headache.....	121	60.5	19	57.6	15.7
Apathy.....	45	22.5	12	36.4	26.7
Irritability.....	19	9.5	9	27.3	47.4
Sleeplessness.....	68	34.0	10	30.3	14.7
Delirium.....	29	14.5	14	42.4	48.3
Sedatives required.....	139	69.5	21	63.6	15.1
Vomiting.....	59	29.5	13	39.4	22.0
Diarrhea.....	5	2.5	1	3.0	20.0
Distention.....	75	37.5	14	42.4	18.7
Icterus.....	8	4.0	2	6.1	25.0
Pulmonary edema.....	14	7.0	12	36.4	85.7
Dehydration.....	21	10.5	10	30.3	47.6
Epistaxis.....	11	5.5	0	0.0	0.0
Hemoptysis.....	10	5.0	2	6.1	20.0
Herpes.....	13	6.5	0	0.0	0.0
Hiccup.....	2	1.0	2	6.1	100.0
Pleurisy.....	139	69.5	24	72.7	17.3
Kahn reaction† (3+ or 4+).....	23	32.4	0	0.0	0.0

* Of the 200 patients, 167 recovered and 33 died. In 6 cases the history was not obtainable.
† For only 71 of the 200 patients was the Kahn reaction studied. Of these 71 patients, 66 recovered and 5 died.

BACTEREMIA

Nonserum Treatment.—Eighteen of the 149 patients who did not receive serum treatment had bacteremia, an incidence of 12.1 per cent. Thirteen of these 18 patients died, a mortality of 72.2 per cent.

In 3 instances the time of onset of bacteremia was known because of previously sterile cultures. The blood of one patient became invaded on the eighth day of illness. The heart blood of another patient contained bacteria when taken on the seventh day post mortem, and that of another patient, when taken on the ninth day post mortem. The cultures of the blood of the other patients gave positive results for type VII pneumococci when the patients were admitted to the hospital.

TABLE 2.—*Data for Patients with Type*

Sex	Age	Year	Out-come	Day of Disease 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No Serum Treatment (Mortality, 72.2 per Cent)																					
F	35	1929	R	..	..	Br	..	..	..	—	..	T	..	..	..	..	..	..	..	..	..
M	36	1936	R	..	..	Br	37 38	8 0	150 12	Br	—	—	—	..	T	..	..	..	..	..	..
M	42	1932	R	..	..	Br	..	7 8	5 4	3 0	—	—	..	..	..	..	..	..	..	..	..
M	42	1933	R	..	..	..	5 8	..	5|8 4|7	..	Br	Br	Br	—	Br T	— *	..	..	..	—	..
F	23	1933	R	..	..	..	—	..	—	..	Br	—	— —	—	..	..	—	—	..	—	Br
M	56	1928	D	..	..	..	..	..	2 3	..	Br	Br	D	..	..	..	..	..	..	..	..
M	45	1929	D	..	..	..	..	..	..	..	..	..	..	..	—	..	..	..	..	Br	D
M	37	1929	D	..	..	..	..	488 424	D	..	..	..	..	..	..	..	..	..	..	..	..
M	48	1929	D	..	..	..	..	..	..	Br	Br	..	..	Br D	..	..	..	..	..	..	..
M	38	1930	D	..	..	1 0	..	..	..	2 0	D	..	..	..	..	..	..	..	..	..	..
M	42	1930	D	..	..	..	..	..	..	..	..	..	..	..	..	Br	Br	2 0	—	..	..
F	29	1930	D	..	..	∞	∞ D	..	..	..	..	..	..	..	..	..	..	..	..	..	..
M	23	1930	D	..	..	—	—	—	..	..	..	— Pm Br D	..	..	..	..	..	..	..	..	..
M	29	1930	D	..	..	7 16	..	..	51 18	∞	Pm Br D	..	..	..	..	..	..	..	..	..	..
M	40	1930	D	..	..	..	..	..	3 2	..	2 0	5 9	D	..	..	..	..	..	..	..	..
F	26	1933	D	..	..	..	..	..	2 3	—	—	—	Br	Br	110 82	368 240	344 288	D	..	..	..
M	50	1933	D	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
M	47	1934	D	..	..	—	—	..	..	Pm 11 25 D	..	..	..	..	..	..	..	..	..	..	..
Serum Treatment (Mortality, 40 per Cent)																					
M	33	1931	R	..	..	..	3 6	18 20 S	2 2 S	— S	— S	— T S	..	..	..	..	..	..	..	..	..
M	55	1932	R	..	..	..	3 0	..	36 32 S	— S	— S	..	.. T	..	..	..	..	..	..	..	..
M	30	1934	R	..	..	..	..	Br	— S	— T S	..	..	..	..	..	..	..	..	..	..	..
M	47	1934	D	..	..	280 230	Br Br S	40 45 S	50 55	Br S	Br S	1,000 S	Pm Br D	..	..	..	..	..	..	..	..
F	19	1934	D	..	..	..	—	..	— S	Pm Br S D	..	..	..	..	..	..	..	..	..	..	..

* R indicates recovered; D, died; —, sterile culture; Pm, postmortem examination of heart blood; numbers, colony counts; ∞, innumerable colonies; Br, positive result of broth culture; T, termination of elevated temperature; S, serum treatment

*Type VII Pneumonia with Bacteremia**

19	20	21	22	23	24	26	30	33	35	52	?	Comments
No Serum Treatment (Mortality, 72.2 per Cent)												
..	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	..	Empyema; pus from chest contained type VII pneumococcus
..	..	..	..	..	..	..	..	..	..	..	T	Pus from chest contained type VII pneumococcus; indeterminate with empyema
..	..	..	..	..	..	..	..	..	..	..	..	
Br	..	—	..	—	..	T	..	..	..	..	..	Bed sore
..	..	..	..	..	..	..	..	..	..	..	..	
D	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	..	Purulent arthritis and pericarditis; culture of material from knee showed type VII pneumococcus
..	..	..	..	..	..	..	..	..	..	..	..	One colony was fished and was not found to contain type VII pneumococcus until sixth day
..	Br	Br	—	..	..	..	—	—	—	—	D	.. Empyema, pericarditis and erysipelas
..	..	..	..	..	..	..	..	..	..	..	..	.. Obesity
..	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	..	Delirium tremens
..	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	..	
..	..	..	..	..	..	..	..	..	..	..	10	Died on day after admission to hospital in alcoholic coma
..	..	..	..	..	..	..	..	..	..	..	11 ..	Alcoholic addict
Serum Treatment (Mortality, 40 per Cent)												
..	..	..	..	..	..	..	..	..	..	..	..	Alcoholic addict; serum: 20,800 units on 5th, 59,200 on 6th, 236,000 on 7th, 400,000 on 8th and 80,000 on 9th day
..	..	..	..	..	..	..	..	..	..	..	..	Empyema; pus from chest contained type VII pneumococcus. Serum: 25,000 units on 6th, 325,000 on 7th and 87,500 on 8th day
..	..	..	..	..	..	..	..	..	..	..	..	Serum: 200,000 units on 6th and 60,000 on 7th day
..	..	..	..	..	..	..	..	..	..	..	..	Icterus; serum: 130,000 units on 4th, 208,000 on 5th, 135,000 on 7th, 265,000 on 8th and 348,000 on 9th day
..	..	..	..	..	..	..	..	..	..	..	..	Septic abortion; serum: 86,000 units on 6th and 80,000 on 7th day

Of the 13 whose blood had less than 50 colonies per cubic centimeter or showed positive results of culture only in broth, 9 died and 4 survived, and of 5 whose blood contained more than 50 colonies per cubic centimeter in one or both plates, 4 died and 1 survived. The following complications developed in the cases of bacteremia: One of the patients whose blood showed 50 colonies or more per cubic centimeter had empyema and recovered. One of the patients whose blood showed a count of less than 50 colonies per cubic centimeter died of purulent pericarditis and arthritis. Another patient had empyema, pericarditis and erysipelas, resulting in death. Another had empyema and recovered.

Serum Treatment.—Among the 5 patients who received serum treatment, 1 received it on the fourth day of illness and the others later. One patient whose colony count was under 50 per cubic centimeter, had empyema and recovered. There were 2 deaths, 1 of which was complicated by septic abortion. Broth culture gave positive results post mortem. The other patient was treated on the fourth day, when the broth culture alone gave positive results, although there had been 280 colonies per cubic centimeter the previous day; this patient had severe icterus. In none of these 5 patients treated with serum did bacteremia develop after serum treatment was begun, except in a patient for whom the only positive result of blood culture was obtained post mortem. This is the patient previously mentioned whose condition was complicated by septic abortion. In table 2 are shown the day of the disease on which a positive result of blood culture was obtained and the number of and changes in the colony counts.

COMPLICATIONS AND ASSOCIATED DISEASES

Nonserum Treatment.—The complications and associated diseases were as follows: There were 6 recognized cases of empyema, and 3 of the patients recovered. Two cases of encapsulated empyema were discovered post mortem. One patient with empyema associated with pericarditis and erisypelas died. Another patient with pericarditis and purulent arthritis died. One patient with purulent arthritis and myositis died. One patient died of meningitis. One patient recovered from a postpneumonia psychosis. Bed sores developed on 4 patients, 2 of whom died, one of the patients who died also having parotitis, and the other, fibroid tumors. Three of the markedly obese patients died. Three patients had diabetes mellitus, and all recovered. One patient had fibrillation during the disease and recovered. Of 8 patients with a history of alcoholic indulgence, 3 died; 2 others entered the hospital with delirium tremens and died; 1 patient with syphilitic heart disease recovered. Three patients had rheumatic heart disease. One patient had carditis and pericarditis, and 1 had mitral insufficiency; both

recovered. One obese patient, previously mentioned, had aortic regurgitation with fibrillation and died. One patient had an intestinal obstruction and died.

Albuminuria occurred in 101 patients, 50.5 per cent of those whose urine was examined. Twenty-three of these patients died. The grade of albuminuria apparently had no influence on the outcome. In 18 patients there was a trace of albuminuria; 7 (38.9 per cent) died. Forty-one patients showed a 1+ reaction of the urine for albumin; 8 (19.5 per cent) died. Forty-two showed a 2+, a 3+ or a 4+ reaction for albumin; 8 (19 per cent) died.

One patient who had been pregnant for seven months recovered, but 1 patient who had pneumonia post partum died. One patient had phlebitis and recovered. One patient died suddenly, with great dyspnea. One patient who had had a septic abortion died. A patient who had a pulmonary abscess died.

Serum Treatment.—Fifty-one patients with type VII pneumonia were treated with serum. Three of these patients were excluded from the series because of serious accompanying conditions. The first patient had rheumatic carditis and pericarditis with effusion with type VII nonbacteremic pneumonia, and recovered. The second of these 3 patients had a septic abortion during type VII pneumonia, with bacteremia, and died. The third patient had type VII pneumonia without bacteremia but with aortic regurgitation and chronic myocarditis and died.

Three patients who died were also excluded from the group of 149 patients who were not given serum treatment. One patient had erysipelas with empyema and type VII pneumonia with bacteremia. The second had intestinal obstruction without bacteremia and the third had a postpartum infection without bacteremia.

The death rate for patients treated without serum, 17.1 per cent $\pm$ 3.1, may be compared with that for those treated with serum, 6.2 per cent $\pm$ 3.4. The ratio of the difference to the standard error is 2.35; or, expressed in another way, there are 981 chances in a thousand that the difference in the death rates is significant. Twelve of the 17 patients who were bacteremic and did not receive serum died, a mortality of 70.6 per cent, as opposed to 1 death among 4 patients treated with serum, a mortality of 25 per cent. The ratio of significance is 1.88, or 940 chances in a thousand. Thirteen (10.1 per cent) of the 129 patients who did not receive serum and who did not have bacteremia died, and 2 of the 44 who received serum treatment died, a mortality of 4.5 per cent. The ratio of significance is 1.38, or 831 chances in a thousand (chart 1).

The 2 patients without bacteremia who received serum and who died were an obese patient who had large fibroid tumors, a bed sore and otitis media and a patient in whom cyanosis and marked dyspnea suddenly developed.

As shown previously type VII pneumonia is moderately severe. Twenty-four of the 55 patients who had severe pneumonia and did not receive serum died, a mortality of 43.6 per cent, and 3 of the 18 who

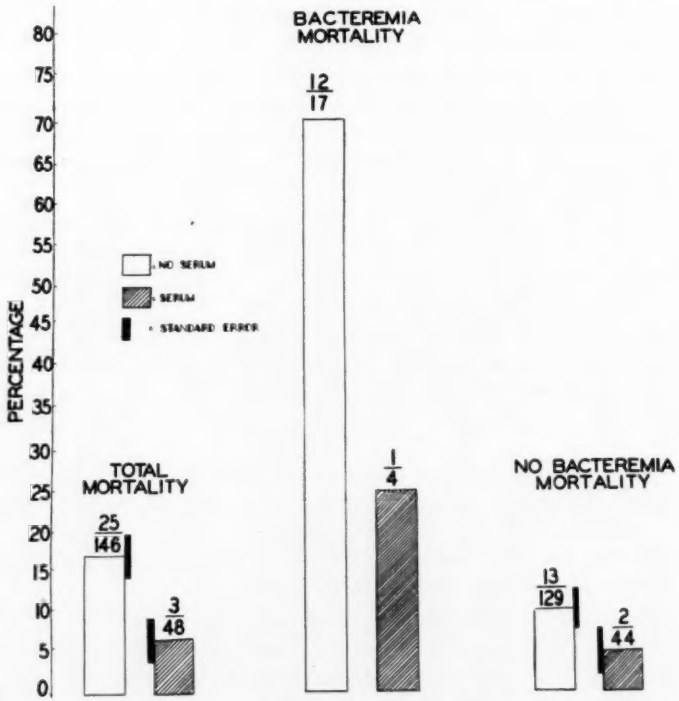

Chart 1.—Type VII pneumonia, showing the effect of serum treatment on the mortality, 1928 to 1935. The ratio of significance for the total mortality is 2.35, or $^{98}1/_{1.000}$. The ratio in the cases in which there was no bacteremia is 1.38, or $^{83}1/_{1.000}$.

had severe pneumonia and received serum died, a mortality of 16.7 per cent (chart 2).

In chart 3 are shown the days after onset that the disease terminated after the commencement of serum treatment (black circles) and the days after onset of termination of disease for patients who did not

receive serum (white circles). The accumulation of the black dots to the left shows the shortening of the illness in the cases in which serum was given. The flags on dots or circles indicate patients with bacteremia.

Combining the cases in which the disease terminated on the same day and on the first day after the patient's admission to the hospital or the commencement of serum treatment, it is found that in 55.6 per cent of the cases in which serum was given and in only 22.7 per cent of the cases in which no serum was given did the disease terminate then. By the conclusion of the second day after the commencement of serum treatment in 33 (73.3 per cent) cases had the illness terminated, whereas

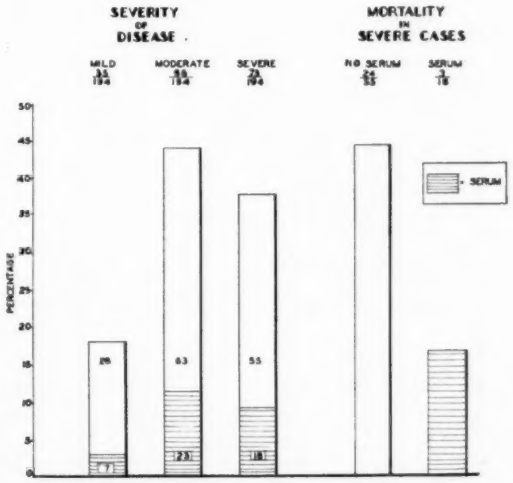

Chart 2.—Summary of data for 194 patients with type VII pneumonia, July 1, 1928, to July 1, 1935 (in 48 cases serum was given, and in 146 cases no serum was given). The data for 6 patients were omitted because of accompanying lethal disease (table 3).

in 45 (only 37.8 per cent) cases in which serum was not given the illness terminated on the second day.

RELATION OF SERUM TREATMENT TO COMPLICATIONS

The group of 14 patients who received serum treatment before the fifth day of the disease had no complications. Five of the 36 patients treated on the fifth day or later had complications, an incidence of 13.9 per cent. One of these died, a mortality of 20 per cent. One patient without complications was omitted because the day of onset of disease was not known. Eighteen of the 149 patients who did not receive serum

had complications, an incidence of 12.1 per cent, but 9 died, a mortality of 50 per cent. The patient who died after treatment on the fifth day or later had otitis media, was obese and had fibroid tumors. In the fatal cases in which no serum was given there were the following complications: embolus (?) and pulmonary abscess; purulent arthritis; meningitis; infected bed sores and parotitis; pericarditis and purulent arthritis; encapsulated empyema; aortic sclerosis and empyema, and empyema, pericarditis and erysipelas.

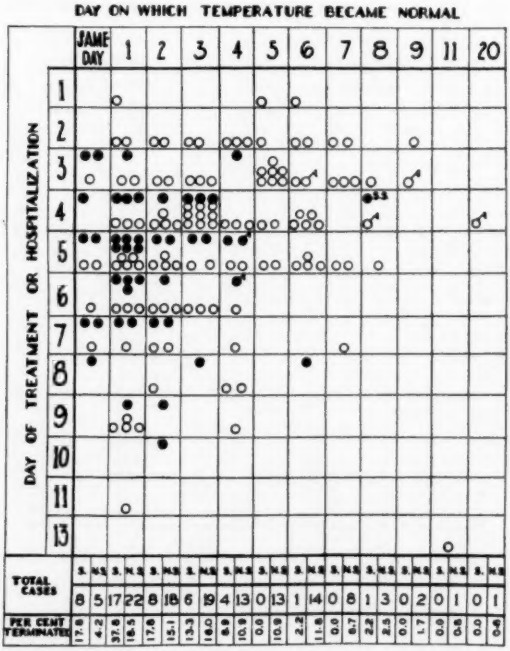

Chart 3.—Duration of illness in cases of type VII pneumonia, July 1, 1928, to July 1, 1935. Recovery was obtained in 45 cases in which serum was given and in 119 cases in which no serum was given. The data for 1 patient who was given serum and for 2 patients who were not given serum are omitted because the date of onset of illness was not known. The black circles indicate patients who received serum; the white circles, patients who did not receive serum; the flags, bacteremia; *S.S.*, serum sickness, with elevation of temperature continuous with pneumonia; *S.*, serum; *N.S.*, no serum. In this chart are recorded the day on which serum treatment was started and that on which the temperature became normal or, in cases in which no serum was given, the day on which the patient was admitted to the hospital and that on which the temperature became normal.

TABLE 3.—*Data for Six Patients with Accompanying Lethal Disease*

Case	Complicating Conditions	Treatment	Invasion of Blood	Severity	Outcome
1	Rheumatic carditis and pericarditis	Serum	No bacteremia	Severe	Recovered
2	Septic abortion	Serum	Bacteremia	Severe	Died
3	Aortic regurgitation and chronic myocarditis with fibrillation.....	Serum	No bacteremia	Severe	Died
4	Erysipelas and empyema.....	No serum	Bacteremia	Severe	Died
5	Intestinal obstruction	No serum	No bacteremia	Moderate	Died
6	Postpartum complications	No serum	No bacteremia	Severe	Died

TABLE 4.—*Type VII Pneumonia and Additional Infections, 1928 to 1935*

Sex	Age	Year	Source of Type VII Pneumococcus	Simultaneous Infections	Successive Infections with	Outcome	
						Serum Treatment	No Serum Treatment
M	34	1929-1930	Lung (suction)	Hemolytic streptococcus (obtained post mortem from heart blood); type III pneumococcus (chains) in sputum	.....	.....	Died
M*	38	1929-1930	Blood culture	Type II pneumococcus (sputum)	.....	.....	Died; received serum for type II pneumonia
M	31	1930-1931	Mouse heart	.....	Bact. pestis caviae Blood culture	.....	Died
M	32	1930-1931	Blood culture	.....	Hemolytic streptococcus Blood culture	.....	Died
M	32	1931-1932	Lung (suction)	.....	Staph. aureus Blood culture	.....	Died
M*	17	1931-1932	Lung (suction)	Type I pneumococcus (sputum)	.....	.....	Recovered; received serum for type I pneumonia
M*	55	1932-1933	Pus from chest Blood culture	Type I pneumococcus (mouse heart)	.....	Recovered	
M	50	1932-1933	Blood culture	.....	Hemolytic streptococcus Heart blood, pericardial fluid, spinal fluid, lung (suction) post mortem	Died	
F	29	1932-1933	Lung (suction)	.....	Hemolytic streptococcus Heart blood, pericardial fluid, lung (suction) post mortem	Died	
M	37	1933-1934	Sputum	Type XIII pneumococcus (sputum)	.....	.....	Recovered
M	49	1934-1935	Pus from chest Blood culture	.....	B. coli Prostatic abscess and blood culture	Died	
F	24	1934-1935	Lung (suction)	.....	B. suipestifer Blood culture	Recovered	

* These cases are included in the series of 200 adults. The others were omitted because the primary infection was indefinite.

ADDITIONAL INFECTIONS

In table 4 are shown the data for 12 patients with type VII pneumonia associated with another organism; 8 of these died and 4 recovered. The source of the pneumococcus in 5 cases was the blood culture and in 5 cases material obtained by pulmonary suction; in 1 case the organism was obtained from the heart blood of a mouse after inoculation with sputum, and in 1 directly from the sputum. In 5 cases the second organism was present at the same time as the pneumococcus, and in 7 cases its appearance succeeded the primary type VII pneumonia.

The complicating organism was Streptococcus haemolyticus in 4 cases; Staphylococcus aureus in 1 case; Bacterium pestis caviae in 1 case; Bacillus suipestifer in 1 case; Bacillus coli in a prostatic abscess in 1 case; Pneumococcus type I in 1 case; Pneumococcus type II in 1 case and Pneumococcus type XIII in 1 case.

Seven patients did not receive serum for type VII pneumonia. One with type I pneumococcus as coinvader received serum for type I but not for type VII pneumonia and recovered. One in whom type II pneumococcus was found in the sputum and type VII in the blood culture received serum for type II but not for type VII pneumonia and died. Five received serum for type VII pneumonia and 2 of them recovered.

When the hemolytic streptococcus was present subsequent to or simultaneously with invasion by the type VII pneumococcus the outcome was uniformly fatal.

CHILDREN

During the seven years 18 cases of type VII pneumonia were observed among children. Of these, 6 were under 2 and 12 were from 2 to 12 years of age. Of the infants under 2 years, 1 who was 8 months old and had meningitis due to type VII pneumococcus died, and another of 3 months with pericardial effusion due to type VII pneumococcus with bacteremia died; neither of the infants received serum. A 10 month, a 19 month and a 20 month old infant recovered without serum. An 11 month old infant received serum on the eleventh day of illness, had empyema and recovered.

All the children over 2 years of age survived, whether they received serum or not. One of the children who was given serum on the tenth day had type VII empyema and recovered.

None of the children received serum sufficiently early to determine whether complications would have been prevented by early serum treatment. The cases are too few to permit the drawing of conclusions as to the value of serum in the treatment of type VII pneumonia in children (table 5).

TABLE 5.—*Type VII Pneumonia in Children, 1928 to 1935*

Sex	Age	Year	Day of Termination of Fever	Blood Culture	Pulmonary Involvement	Comments	Outcome
				No Serum Treatment (15 Cases)			
M	8 mo.	1929-1930	10th (died)	None	Upper and middle lobes of right lung	Meningitis, type VII pneumococcus	Died
F	5½ yr.	1929-1930	9th	None	Pleurisy, lower lobe of right lung	.....	Recovered
M	6 yr.	1929-1930	8th	None	Lower lobe of right lung	.....	Recovered
M	20 mo.	1930-1931	7th	Sterile	Upper lobe of right lung	Meningism	Recovered
M	5 yr.	1930-1931	5th	Sterile	Pleurisy, lower lobe of left lung	.....	Recovered
M	6 yr.	1930-1931	9th	Sterile	Lower lobe of left lung	.....	Recovered
M	11 yr.	1930-1931	7th	Sterile	Pleurisy, lower lobe of left lung	Lung suction; type VII pneumococcus	Recovered
M	9 yr.	1931-1932	7th	Sterile	Lower lobe of left lung	Lung suction; type VII pneumococcus; delirium	Recovered
F	19 mo.	1931-1932	9th	None	Upper and lower lobes of left lung	.....	Recovered
M	5 yr.	1931-1932	6th	Sterile	Upper lobe of right lung	Lung suction; type VII pneumococcus; purulent otitis media	Recovered
M	3 mo.	1932-1933	17th (died)	Heart blood post mortem contained type VII pneumococcus	Pleurisy, upper lobe of right lung	Postmortem pericardial fluid; type VII pneumococcus	Died
M	4 yr.	1932-1933	3d	Sterile	Lower lobe of right lung	.....	Recovered
M	10 mo.	1933-1934	Onset indefinite	None	Bronchopneumonia	Rickets	Recovered
M	10 yr.	1933-1934	7th	None	Lower lobe of left lung	Lung suction; type VII pneumococcus	Recovered
F	7 yr.	1933-1934	5th	Sterile	Pleurisy, upper lobe of left lung	.....	Recovered
				Serum Treatment (3 Cases)			
F	11 mo.	1930-1931	? Indeterminate, with empyema on admission	Sterile	Pleurisy, upper lobe of left lung	Empyema; type VII pneumococcus; transfusion; lung suction, type VII pneumococcus; rickets; serum given on 11th day	Recovered
M	5 yr.	1930-1931	7th	Sterile	Pleurisy, lower lobe of right lung	Lung suction; type VII pneumococcus; serum given on 6th day	Recovered
M	7 yr.	1931-1932	14th	Sterile	Pleurisy, lower lobe of right lung	Empyema; type VII pneumococcus; meningism; serum given on 10th day	Recovered

CONCLUSION

It appears as the result of these studies that among the patients who received serum the mortality was significantly reduced, as shown in chart 1, and that the duration of illness was shortened, even when serum treatment was begun on the fifth, sixth or seventh day of illness (chart 3).

The patients to whom serum was administered before the fifth day of illness had no complications. For the group of patients who received serum on the fifth day or later and for the group who were not given serum the incidence of complications was approximately the same, but the mortality among those with complications who were treated on the fifth day or later was lower than the mortality among the corresponding group of patients who did not receive serum treatment.

FUNCTIONAL ACTIVITY OF RENAL EPITHELIUM IN CERTAIN TYPES OF NEPHRITIS

AS INDICATED BY SECRETION OF AMMONIA

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Since ammonia appears to be elaborated by the renal tubules, the activity of its production might, if looked at from a proper theoretical point of view, throw light on the functional state of the tubular division of the renal parenchyma; an altered functional state with nephritis might be reflected in a corresponding alteration of the activity of production of ammonia.

The suggestion for the present study came with the development of a new view concerning the mechanism which results in the production of ammonia by the kidney.[1] According to this view, the production of ammonia by the renal tubules is stimulated by and serves to neutralize the acid residue which remains to flow through the tubules after resorption of the alkaline threshold moiety from the glomerular filtrate.[2] In contrast to this theory is the classic concept, which assumes that production of ammonia responds to the requirements of the body for the excretion of acids, which could not otherwise be excreted in the urine without drawing from the body an excessive amount of the essential alkaline elements. It further assumes that the production of ammonia is diminished when it is desirable for the body to become rid of excess fixed base.

Some of my reasons for dropping this view were as follows: 1. The production of ammonia is not necessarily increased when there is a surplus of acid in the body to be excreted. Such an exception occurs after administration of potassium chloride, when because of the rapidity of the excretion of potassium into the urine a surplus of chloride remains. And this surplus is perfectly analogous to that which remains

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1. Briggs, A. P.: (*a*) The Acidosis of Nephritis: Its Clinical Significance, Arch. Int. Med. **49**:56 (Jan.) 1932; (*b*) Excretion of Ammonia and Neutrality Regulation, J. Biol. Chem. **104**:231 (Feb.) 1934.

2. This view has been worded to fit the current filtration-resorption theory of urinary secretion. If it should be found that waste acid is secreted by the tubules, it would still appear that stimulation of the production of ammonia results from irritation of acid.

after administration of calcium chloride because of excretion of calcium by the intestine. According to the classic base-regulatory theory, production of ammonia should be increased after administration of either potassium chloride or calcium chloride. This is not true. According to the stimulus-response theory, an increase should be observed only after the administration of calcium chloride, and this is true. 2. The production of ammonia is not necessarily decreased when the body is loaded with a surplus of fixed base. Such an exception has been observed to follow the administration of diabasic sodium phosphate, when increased production of ammonia was associated with more rapid secretion of phosphate than of sodium. Production of ammonia in this instance is again understandable from the stimulus-response point of view and not from the base-regulatory concept. 3. Diuresis from water, urea or other neutral substances does not increase the formation of ammonia, even though the bicarbonate content of the plasma is seriously depleted. This is a flat contradiction to the base-regulatory theory, but it is in harmony with the view taken here, for the diuresis prevents the formation of an acid residue within the tubules.

All of these special circumstances, as well as all other experimental maneuvers, show fluctuations of excess acid in the urine to be accompanied with a similar fluctuation of the amount of ammonia.

It should be pointed out, in addition to what has already been said, that the classic concept of the production of ammonia is not at all compatible with the current filtration-resorption view of urinary secretion. For the various acids of the urine are thought to be filtered into the tubule passively by the glomerulus; the production of ammonia can hardly have anything to do with filtration of acid. Conceivably, resorption of fixed base might be facilitated by secretion of ammonia, but far too much base is resorbed to be accounted for by the ammonia produced, even with a highly acid ash diet. Moreover, with a change to an alkaline ash diet, the quantity of base resorbed is thought to remain unchanged, while the secretion of ammonia falls off to a minimum.[3]

It is proposed here to show further examples of the parallelism between the amount of ammonia formed by the kidney and the amount of excess acid excreted. Then, with an established normal relationship for comparison, a number of observations will be reported showing the response, in production of ammonia to excess acid, with certain types of nephritis.

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3. Peters, J. P.: Body Water, Springfield, Ill., Charles C. Thomas, Publisher, 1935. Peters has criticized my views and has stated the conclusion that they should be rejected. Actually he has failed to point out any instance in which a change in excess of acid over fixed base in the urine is not accompanied with a similar change in secretion of ammonia. His discussion of the inconsistencies of the accepted view seemed incomplete and far from convincing.

EXPERIMENTAL METHOD

The normal subjects of this study were persons associated with the laboratory or patients showing no evidence of renal disease. The two groups of nephritic patients studied were (1) those giving clinical and laboratory evidence of an advanced stage of arteriosclerotic or hemorrhagic nephritis (these are referred to as patients with contracted kidneys) and (2) patients with the nephrotic syndrome.

Specimens of urine were collected over various periods during the day or night. Usually before a daytime study was made an acid or acid residue salt was taken by mouth, as indicated in the tables. The importance of preventing an alkaline tide during the period of study is obvious, for the excess of base excreted during this phase might approximately balance the excess of acid excreted during the remaining part of the period and the ammonia excreted during the latter phase would appear out of all proportion to a slight excess of acid for the total period. A continuous secretion of excess acid was assumed for the night periods.

In the collection of urine from women, either the vulva was first swabbed with physiologic solution of sodium chloride or the specimen was obtained by catheter.

Chloroform and thymol were used as preservatives.

Chemical Methods.—Chloride was determined by a modified Volhard-Harvey titration and sulfate by the method of Fiske. For phosphate the uranium titration was employed. Phosphate was calculated as monovalent, for the reason that administration of a large quantity of phosphoric acid [1a] stimulates the production of sufficient ammonia to reduce the acidity of the urine to approximately p_H 5, i. e., the vicinity of the point at which 1 hydrogen ion is completely neutralized.

For the same reason it was assumed that organic acid weaker than monobasic phosphate would have relatively little excitation for the production of ammonia; the strong organic acid reported is that fraction which titrated between the acidities of fifteenth-molar potassium phosphate and hundredth-molar citric acid. Since the purpose was to develop a technic which would be applicable to albuminous urine, such as is obtained from nephritic patients, it was desirable to remove albumin more completely than by acidification and heat. A little study indicated that a preliminary precipitation with zinc hydroxide removes albumin completely and serves also to remove phosphate, as is ordinarily done by calcium hydroxide. A little lactic acid is removed by this precipitation, and appreciable quantities of tartaric and citric acid may be removed; however, a comparison was made with the usual calcium hydroxide filtrate for normal urine, and similar values for strong organic acid were obtained. The zinc filtrate was found to be practically free from pigment, so that good color matches were obtained with the indicators employed. Skatole, if present, does pass into the zinc filtrate and interferes by producing a reddish coloration. In order to determine the correction for creatinine, a solution of creatinine and zinc chloride was precipitated and titrated as will be outlined presently. It was found that about 43 per cent of the creatinine was titrated over the range taken for strong organic acid.

The procedure employed was as follows: From 10 to 30 cc. of urine was diluted with water and 10 cc. of half-normal sodium hydroxide to a volume of 40 cc., precipitated with 10 cc. of a 10 per cent solution of zinc sulfate and filtered. One 15 cc. aliquot of the phosphate-free and protein-free filtrate was titrated with tenth-normal hydrochloric acid, methyl red being used as indicator, to match a standard containing the same amount of indicator in a similar tube and diluted with fifteenth-molar potassium phosphate. Comparisons were made

by looking down through the tubes at a white plate. Another 15 cc. aliquot was similarly titrated to match a standard of hundredth-molar citric acid, bromphenol blue being used as indicator.

The difference between the two titrations was taken as the basis for the calculation. A correction was made for the blank titration on the reagents.

Fixed base was determined by a technic essentially similar to that of Stadie and Ross (phosphate was removed with ferric sulfate at p_H 5). For ammonia the aeration technic of Cullen and Van Slyke was employed and for creatinine the usual Folin and Wu method.

In calculating the excess acid, no consideration was given to the influence of creatinine as an organic base. The omission of this organic base tends to balance the omission of weak organic acid.

It became obvious early in the study that the ammonia ratio was influenced by the rate of flow of urine. The rate has therefore been calculated and is expressed in cubic centimeters per kilogram per hour. This expression was chosen for the reason that kidney weight, body weight and urine volume increase together during growth.

The ammonia ratio was calculated as:

$$\frac{NH_3}{(Cl + H_2PO_4 + SO_4 + \text{strong organic acid}) - (\text{fixed base})}$$

All the values were expressed as milliequivalents.

RESULTS

Inspection of the results for normal subjects in table 1 reveals that there is no good correlation between the quantity of excess acid and the ammonia ratio. It may be noticed also that the ammonia ratio is low when the rate of flow is fast and high when the rate is slow.

The relation between the rate of flow and the ammonia ratio is shown better in the accompanying chart. Here it becomes apparent that there is a definite relation between excess acid, the production of ammonia and the rate of flow of urine. That the ratio is so influenced by a local factor, the rate of flow, is entirely meaningless from the base-regulatory point of view; it is, however, what might be expected from the stimulus-response point of view. For with a more rapid rate, acid flowing through the tubules makes less intimate contact with epithelium.

At the slower rates the excess of strong acid is about 100 per cent neutralized. This finding, at slow rates, of a quantity of ammonia approximately equal to the excess of strong acid is evidence that the factors creatinine and weak organic acid, omitted in the calculation, are not significant or tend to balance.

Ratios obtained after the administration of large quantities of ammonium salts are not noticeably high; they fall in with the rest of the values for normal subjects given in the chart. This result might be anticipated, for most of the ammonia is converted to urea, and a slight increase of ammonia in the plasma and glomerular filtrate should result in only a corresponding decrease in the supplementary ammonia

TABLE 1.—*Urinary Acids and Bases and Ammonia Ratios at Various Rates of Flow*

Test	Subject	Chlorine	Sulfate	Phosphate	Strong Organic Acid	Fixed Base	Excess Acid	Ammonia	Ratio, %	Rate of Flow†	Comments
1	A.P.B.	19.15	6.50	5.77	4.13	25.63	9.92	9.75	98	0.40	Night urine
2	A.P.B.	23.30	5.33	5.17	7.40	30.20	11.00	11.32	103	0.38	Night urine
3	A.P.B.	15.70	4.23	3.92	6.75	20.90	9.70	7.13	74	0.70	Night urine
4	A.P.B.	21.92	1.35	4.26	11.58	29.30	9.81	9.02	92	0.61	Night urine
5	A.P.B.	20.06	1.75	0.66	2.83	20.02	5.28	3.81	72	1.67	30 cc. of normal hydrochloric acid
6	A.P.B.	5.64	0.43	0.42	2.04	7.18	1.35	0.84	62	2.00	20 cc. of normal hydrochloric acid
7	A.P.B.	5.63	0.30	0.42	2.52	7.11	1.76	1.06	60	2.24	25 cc. of normal hydrochloric acid
8	A.P.B.	27.18	2.11	0.53	1.96	29.80	1.98	1.50	76	0.93	25 cc. of normal hydrochloric acid
9	A.P.B.	9.35	1.49	1.78	1.22	10.92	2.92	2.48	85	0.98	60 cc. of tenth-molar phosphoric acid
10	A.P.B.	9.63	0.74	1.53	1.43	11.35	1.98	1.59	80	1.46	60 cc. of tenth-molar phosphoric acid
11	A.P.B.	13.16	0.73	2.09	2.61	15.70	2.89	2.24	78	1.37	60 cc. of tenth-molar phosphoric acid
12	A.P.B.	27.17	3.72	0.75	2.17	24.51	9.30	5.03	54	1.67	20 cc. of 5% ammonium sulfate
13	A.P.B.	20.10	7.17	5.28	5.23	26.56	11.22	9.49	84	0.39	Night urine
14	A.P.B.	17.30	1.15	1.20	2.38	20.40	1.63	1.40	86	0.58	20 cc. of normal hydrochloric acid
15	A.P.B.	22.31	4.08	1.84	1.52	22.40	7.35	6.98	95	0.35	Night urine
16	A.P.B.	22.88	1.43	1.40	3.55	26.12	3.14	2.13	68	0.67	5 Gm. of ammonium chloride
17	A.P.B.	29.00	2.74	0.60	0.97	30.64	2.67	2.35	88	0.70	4 Gm. of ammonium chloride
18	A.P.B.	14.25	2.61	0.93	2.63	16.25	4.17	3.46	83	1.00	3 Gm. of ammonium sulfate
19	A.P.B.	19.50	4.43	3.54	3.41	25.50	5.38	5.66	105	0.36	Night urine
20	A.P.B.	30.90	2.20	1.10	1.55	30.21	5.54	4.97	90	0.90	5 Gm. of ammonium chloride
21	A.P.B.	20.08	0.90	0.38	1.48	18.60	4.24	3.03	72	1.90	7 Gm. of ammonium chloride
22	E.	20.55	1.44	1.38	1.48	20.50	4.35	4.05	93	0.73	Exophthalmic goiter
23	E.	17.02	4.09	1.57	3.81	21.90	4.59	3.63	79	0.84	Exophthalmic goiter
24	J.W.	17.55	3.48	3.08	4.05	20.05	8.11	7.37	91	0.40	Arthritis
25	G.O.B.	15.20	4.08	3.51	1.45	21.00	3.24	3.52	108	0.23	Night urine
26	J.A.	16.80	3.56	2.52	2.73	23.70	1.91	1.75	92	0.51	Aged 12 years
27	I.S.	14.70	4.39	3.42	1.86	18.58	5.79	4.62	80	1.34	Aged 7 years
28	I.S.	15.83	3.68	3.25	2.17	20.22	4.71	3.43	73	1.48	
29	M.S.	13.51	4.22	7.74	2.40	14.76	13.11	8.48	65	1.38	Aged 3 years
30	M.S.	21.33	3.77	4.18	2.58	18.10	13.76	8.48	62	1.52	
31	G.B.Jr.	17.50	2.59	2.22	2.29	21.95	2.65	2.11	80	1.08	Aged 7 years

* The results in tables 1 to 3 are expressed as milliequivalents per hundred cubic centimeters of urine.

† The rate of flow of urine is given in cubic centimeters per kilogram per hour.

produced for neutralization. The administration of ammonium chloride provides a convenient way of establishing a large excess of strong acid which can be accurately determinned.

Tubular Function in Nephritis with Contracted Kidneys.—Ratios obtained for patients with this type of nephritis are shown in table 2. On the chart they are observed to fall to the left of the normal zone, the zone of low response.

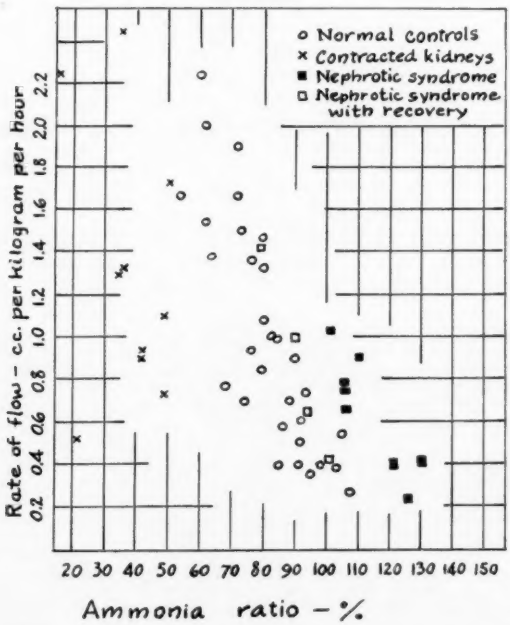
o Normal controls
× Contracted kidneys
■ Nephrotic syndrome
□ Nephrotic syndrome with recovery
Rate of flow - c.c. per kilogram per hour
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2
20 30 40 50 60 70 80 90 100 110 120 130 140 150
Ammonia ratio - %

Chart showing the relation between excess acid, production of ammonia and rate of flow of urine in health and in certain types of nephritis.

At first glance these results appear to offer nothing more than confirmation of other studies showing "poor" production of ammonia in advanced nephritis. Thus, Van Slyke and his associates [4] observed low ratios for $\frac{\text{ammonia}}{\text{titratable acidity}}$, and Magnus-Levy [5] observed low ratios for $\frac{\text{ammonia}}{\text{total nitrogen}}$.

4. Van Slyke, D.D.; Linder, G. C.; Hiller, A.; Leiter, L., and McIntosh, J. F.: The Excretion of Ammonia and Titratable Acid in Nephritis, J. Clin. Investigation **2**:255 (Feb.) 1926.

5. Magnus-Levy, A.: Das Ammoniak bei der Nephrose, Ztschr. f. klin. Med. **112**:256, 1930.

However, it is rather obvious that the passing of a given volume of urine through the renal remnant of a nephritic patient requires a much greater speed than would be required for it to pass through a normal kidney with many more tubules. It is not unlikely, therefore, that an expression for approximate tubular rate of flow, if such could be obtained, would throw the nephritic ratios up into the normal zone.

This suggestion that the epithelium of the renal remnant in advanced nephritis is functioning in a normal manner demands a review of other evidence available. The manner of resorption of threshold material is of particular interest.

One of the characteristic findings with the destruction of much renal parenchyma is an increase in the urinary volume, particularly of the night portion. The explanation of this phenomenon may be that

TABLE 2.—*Ammonia Ratios for Subjects with Contracted Kidneys*

Subject	Date	Chlorine	Sulfate	Phosphate	Strong Organic Acid	Fixed Base	Excess Acid	Ammonia	Ratio, %	Rate of Flow	Nonprotein Nitrogen	Comments
F.O.	10/ 5/34	4.20	0.55	0.60	0.69	4.26	1.78	0.87	49	1.10	132	
G.O.	3/26/35	11.50	1.61	1.19	2.32	11.97	4.65	1.95	42	0.93		
	3/27/35	14.32	0.50	1.17	2.03	14.00	4.02	1.97	49	0.73	78	
N.T.	12/ 1/34	2.44	1.14	0.98	1.78	4.21	2.13	0.75	35	2.44	67	
F.H.	4/15/35	3.58	1.10	1.80	1.46	6.46	1.48	0.76	51	1.72	83	
H.D.	4/16/35	6.76	1.13	1.03	2.18	8.91	2.19	0.92	42	0.89	108	
T.P.	4/ 6/35	10.37	1.34	2.10	2.83	15.25	1.39	0.52	37	1.35	...	Pernicious anemia and nephritis
S.D.	10/27/36	5.66	2.02	0.61	1.78	8.06	2.01	0.42	21	0.57	110	
M.M.	11/ 5/36	7.14	1.22	0.51	1.98	8.53	2.32	0.80	34	1.24	90	
R.W.	11/12/36	7.13	1.56	0.69	1.52	9.07	1.83	0.33	18	2.23	120	

surviving glomeruli carry on compensatory overactivity and form an abnormal quantity of filtrate; then with an increased rate of flow through the tubules, more water escapes, because of the mechanical handicap to resorption, than would normally be the case. The hypertrophied appearance of surviving glomeruli and the dilatation of surviving tubules give evidence in favor of this suggestion.

Resorption of dextrose is practically unimpaired even in advanced nephritis.

Functional activity in resorption of chloride is best judged by the level maintained in the body fluids. The chloride content of the plasma in nephritis is low as a result of vomiting and at times from other causes, but in the absence of vomiting it is not usually low.[6]

6. Atchley, D. W., and Benedict, E. M.: Serum Electrolyte Studies in Normal and Pathological Conditions: Pneumonia, Renal Edema, Cardiac Edema, Uremic and Diabetic Acidosis, J. Clin. Investigation **9**:265 (Oct.) 1930. Greene, C. H.; Wakefield, E. G.; Power, M. H., and Keith, N. M.: The Electrolyte Distribution and the Acid-Base Equilibrium in the Serum in Cases of Nephritis and Nephritic Acidosis, Biochem. J. **26**:1377, 1932. Briggs.[1a]

Resorption of fixed base, like resorption of water, is not quite perfect. Even in the absence of vomiting, the level of fixed base in the plasma is found to be most frequently between 145 and 150 milliequivalents per liter,[6] whereas in health the fluctuations are most frequently between 150 and 155 milliequivalents per liter. In a previous publication [1] it was pointed out that this slight defect in resorption of fixed base might well be a diuretic effect, since diuresis always causes the waste of some fixed base.

It appears then, so far as resorption of threshold material is concerned, that there is no good evidence of impaired functional activity of the renal epithelium in this type of nephritis.

This conclusion should not be surprising, for each surviving tubule carries the burden of resorbing the threshold material filtered by only a single glomerulus. And a good state of nutrition should be preserved in the tubule so long as the circulation in the glomerulus is adequate for filtration.

The one defect which does exist, the excessive rate of flow, accounts for the slightly impaired resorption of water and fixed base and also for the low ammonia ratios. Surely it is an unnecessary assumption to attribute the slightly impaired conservation of fixed base in nephritis to the "poor" production of ammonia by the kidneys.

Tubular Function in Patients with the Nephrotic Syndrome.—In contrast to the low ratios obtained for patients with contracted kidneys are the high ratios for those with the nephrotic syndrome (table 3). The rates of flow are observed to be low, but not lower than for some of the normal subjects with restriction of fluid.

These high ratios for nephrosis consequently fall to the right of the normal zone on the chart. This is the zone of excessive functional response. Ratios from these same subjects after recovery are observed to fall within the normal zone.

Studies of the ratio $\frac{\text{ammonia}}{\text{titratable acidity}}$ have not brought out any abnormality of secretion of ammonia in the nephrotic syndrome.[3] Magnus-Levy [5] has, however, observed in nephrosis high ratios for $\frac{\text{ammonia}}{\text{total nitrogen}}$ in the urine. And these results were thought by him to indicate that the kidney in nephrosis responds as usual to metabolic changes, but because of a state of irritation, an overproduction of ammonia results.

The interpretation which I have offered is much the same as that of Magnus-Levy. It is suggested that the tubular epithelium in nephrosis responds as in health to excess strong acid, but possibly it responds also to weak organic acid, because of a state of irritation.

The notion that cells with so-called degenerative changes, such as are observed in the tubular epithelium in nephrosis, might function with excessive activity is of course not a new one; cytologists from

time to time have called attention to this possibility.[7] Sufficient consideration has not, however, been given to the possible clinical application of this conception.

The nephrotic syndrome is characterized clinically by scanty urine and the development of edema without retention of waste substances. The chief cause of the edema appears to be albuminuria, with resulting depletion of the protein content of the plasma. However, these patients may, without any changes in diet or medication or detectable change in the protein content of the plasma, show marked fluctuations in water balance. Such observations suggest the possibility of some other renal factor aside from that which permits albuminuria.

TABLE 3.—*Ammonia Ratios for Subjects with Nephrosis*

Subject	Date	Chlorine	Sulfate	Phosphate	Strong Organic Acid	Fixed Base	Excess Acid	Ammonia	Ratio, %	Rate of Flow	Comments
W.H.	9/18/34	3.55	1.51	1.85	1.75	4.68	3.98	4.97	125	0.22	Nephrotic syndrome; chronic hemorrhagic nephritis
	9/22/34	2.44	2.49	1.24	1.61	5.04	2.74	3.32	121	0.40	
	12/13/34	9.85	1.09	2.27	2.32	7.08	8.45	9.34	110	0.91	Much less edema; ratio still high
	12/24/34	9.79	0.41	0.96	2.68	9.88	3.96	3.72	94	0.65	Free from edema normal ratios
	12/26/34	11.60	0.52	1.22	3.38	12.59	4.13	4.17	101	0.42	
D.B.	10/15/34	5.00	12.10	3.30	4.20	15.62	8.98	11.18	130	0.42	Nephrosis; otitis media
M.D.	11/ 9/34	9.12	5.25	4.24	2.62	12.00	9.23	9.75	106	0.79	Nephrosis; maxillary sinusitis
	12/29/34	15.70	2.24	2.99	3.24	19.90	4.27	3.82	90	1.00	Free from edema
E.K.	9/28/35	1.06	9.48	7.72	6.14	3.31	21.09	22.60	107	0.67	Nephrosis; tonsillitis sinusitis
	9/30/35	0.78	13.72	7.71	6.32	5.85	21.68	23.20	107	0.78	
	10/ 4/35	26.90	3.60	3.25	3.03	16.76	20.02	20.63	102	1.25	
	1/30/36	14.78	4.73	4.61	3.46	15.98	11.60	9.14	79	1.41	Nearly free from edema

Studies of urea clearance[8] indicate that glomerular filtration may remain normal throughout the course of true nephrosis and that it is usually normal in the early edematous stages of the nephrotic syndrome of hemorrhagic nephritis.

The association of normal glomerular filtration with scanty urine is difficult to explain except on a basis of excessive tubular resorption. It has been suggested[9] that degenerative changes in the tubules might

7. Oliver, Jean: A Further Study of the Regenerated Epithelium in Chronic Uranium Nephritis, J. Exper. Med. **23**:301 (March) 1916.

8. Van Slyke, D. D.; Stillman, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; Möller, E.; MacKay, E. M.; Hannon, E. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257, 1930.

9. Cushing, A. R.: The Secretion of the Urine, ed. 2, London, Longmans, Green & Co., 1926.

result in the loss of integrity for separation of threshold substances and permit back-diffusion of filtrate. Such a circumstance, however, could not account for the scanty urine in nephrosis, for the result would be the same as from diminished glomerular filtration—imperfect excretion of urea and other waste material, which does not occur.

Certainly the simplest and most consistent explanation assumes only what is suggested by the high ammonia ratios: excessive resorption of the threshold substances. The abnormal return of water and sodium salts to the body therefore provides a contributory cause for edema in the nephrotic syndrome.

SUMMARY AND CONCLUSIONS

Additional observations have been made showing the parallelism between ammonia and excess of acid over fixed base secreted in the urine.

It has been observed that the ratio of ammonia to excess acid is influenced by the rate of flow of urine through the tubules in a manner which is in harmony with my stimulus-response view.

From this point of view the ammonia ratio has been studied in certain types of nephritis as an index of functional activity of the renal epithelium.

In attempting to interpret the results it has been concluded that surviving epithelium of contracted kidneys may function in a fairly normal manner; that the high ratios observed in the nephrotic syndrome are best explained on a basis of excessive functional activity, due to a state of irritation, and that excessive resorption of water and sodium salts may be a contributory factor in the production of edema.

THALAMIC SYNDROME

SYNDROME OF THE POSTERIOR CEREBRAL ARTERY; A REVIEW

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BALTIMORE

The thalamic syndrome was first described by Dejerine and Egger [1] in 1903. Perhaps the subject can best be introduced by a description of the first classic case.

Early one spring morning in the year 1902 an elderly woman named Madame Jossaume ate breakfast with her usual relish. Afterward she sat back and perhaps mused over some of the events of her seventy-six years of life. Suddenly she felt dizzy. She fell to her knees, and everything seemed to swim about her. Then she began to vomit violently. She did not faint but was unable to get up without help. The family put her to bed. She was seized with an imperative desire to micturate without being able to do so. She tried to move her extremities but found that her left arm and leg were leaden and inert.

Fifteen days later the paralysis began to disappear, and soon Madame Jossaume could move her arms and legs almost as well as ever. She was at all times able to show her teeth, close her eyes and wrinkle her forehead. Her mouth never deviated to one side or the other. However, she was far from comfortable. The urinary retention had been succeeded by frequent irresistible calls to micturate. Furthermore, since her attack she had been tormented day and night by sharp continuous pains over the left side of the face, radiating down the left arm and over the whole left side of the body. When the pain was of greatest severity, she felt as though her left eye were being gouged out and torn from its socket. Intense burning and crawling sensations passed over the left temple, up the left ear and the left nostril and over the left half of the tongue. The illness began in April. In July the patient was suffering as much as ever; so she was taken to the Salpêtrière Hospital in Paris, where she was first seen by Dejerine.

"In spite of her seventy-six years," reads his note, "the patient shows no signs of senility." He began his examination by testing touch perception over her left hand with a water-color brush. She did not feel it at all. He tried various parts of her hand and the lower part of her forearm. Still no response! He moved up her arm, and there was now a faint perception of touch. There was hypesthesia of the arm, which diminished as the shoulder was approached. A corresponding state of affairs was found in the left foot and leg. The patient was unable to feel the brush on the left half of the face. The mucous membrane on the left side of the mouth, palate, pharynx and tongue was hypesthetic, and the same was true of the cornea and conjunctiva of the left eye.

Armed with a pin, Dejerine now explored his patient's sensibility to pain. Apparently some one had tried this immediately after her attack, three months

From the subdepartment of Neurology, the Johns Hopkins University.

1. Dejerine, J., and Egger, M.: Contribution à l'étude de la physiologie pathologique de l'incoordination motrice, Rev. neurol. **11**:397, 1903.

previously. At that time the pinprick elicited dysesthesia, creeping, crawling and other disagreeable sensations over the left half of the body but no localized sensation of pain at the point stimulated. The patient, however, felt Professor Dejerine's pinpricks for what they were, though the sensation was less sharp over the hand and foot than over the more proximal portions of the extremities. It is interesting here in the light of later work to mark well that no mention is made of any change in the threshold to pain. Furthermore, once the threshold was overcome (regardless of whether or not it was raised), the patient did not experience dysesthesia of a violence out of proportion to the stimulus; rather she felt the pinprick less sharply than on the good side.

Dejerine tried the effect of a warm stimulus (50 C.) over the same areas and noted that the trunk and face were more sensitive to heat than the extremities. He apparently based this finding on a lag in response of fifteen seconds over the hand and of from fifteen to twenty-five seconds over the foot. On the forearm the delay was only three or four seconds, and over the arm and thigh the stimulus was felt immediately, although not as intensely as on the right side. He further observed that although the left side of the face was hypesthetic to heat it was hyperesthetic to cold. He did not, however, give details.

Madame Jossaume was barely able to feel pressure on her fingers, though as it was applied to more proximal portions of her arm she could feel it better. When the tuning fork was placed on bony prominences of the abnormal side of the body, she felt no vibration but instead complained of an intense burning sensation, even over those parts where anesthesia to heat had been most marked.

Investigation of the sense of limb position gave striking results. Apparently the patient had not the remotest idea that the position of the arm was changed, whether the joints were flexed, extended, abducted, adducted, rotated, pronated or supinated. The loss of the sense of passive movement in the leg was serious but not as profound. She knew, for instance, that her toes were being moved, but she could not tell in what direction.

Astereognosis of the left hand was complete. The patient was unable to recognize either the form or the physical properties of objects placed in her hand and could not name the objects. She had completely lost her sense of differences in weight.

Passing now to a review of the motor system, Dejerine found that all the movements of the extremities were entirely preserved. The muscles had not suffered either contracture or loss of tone. Muscle strength, however, was considerably weakened in both the left arm and the left leg. There was slight paralysis of the left side of the mouth but no evidence that emotional mimicry was in any way affected.

The ankle and patellar tendon reflexes were exaggerated on both sides but more so on the left. The deep reflexes in the arms were equal on the two sides. There was no true Babinski sign on either side, although plantar stimulation resulted in dorsal flexion of both feet.

Dejerine noticed that from time to time the patient's left arm was agitated by a choreic tremor, consisting of small movements of pronation and supination and of flexion and extension of the arm, hand and fingers. Conversational allusion to her arm caused the tremor to appear and the patient was unable to control it. Dejerine found that the only way to stop the tremor was to divert her attention. A certain awkwardness of the left side was manifest, but after some hesitation she was able to touch her nose with her eyes closed. Some diminution of hearing was noted on the left and a sensation of dryness of the mouth on the left.

These are the facts in the order that Dejerine uncovered them. Another similar case was brought to his attention, and he reported both at a meeting of the Paris Neurologic Society in April 1903. His diagnosis was lesion of the optic thalamus. A few months later Thomas and Chiray (1904) presented two cases in which there were almost identical symptoms and proposed the thalamic syndrome.

A year later Madame Jossaume died. The autopsy must have aroused considerable interest. The meninges and hemispheres were normal. Examination of the brain stem revealed that the right pyramid was larger than the left. The knife was then passed through the brain in a horizontal plane from the frontal to the occipital lobe, just grazing the uppermost part of the corpus striatum and thalamus. When the top section of the brain was lifted off, a brownish-yellowish area, about as large as a hazelnut was revealed in the posterior and lateral part of the right thalamus.

In 1906 Dejerine and Roussy [2] described a symptom complex dependent on a lesion exactly localized in the optic thalamus. The hemiplegia develops in a mild manner. If consciousness is lost at all it is only for a short time. The paralysis is always slight, without the development of contracture, and is rapidly regressive. The ability to move the extremities is usually restored quickly. Hypotonicity of the muscles and diminution of muscular strength are noted. The deep reflexes are a little exaggerated, but there is seldom a Babinski sign.

Mild hemiataxia is considered to be dependent on loss of sensation and related to more or less complete astereognosis. Hemichorea and athetosis are frequent. Tremor was observed in one case.

The sensory changes are both subjective and objective. There is superficial anesthesia which is accompanied with persistent and marked loss of deep sensation. Touch, pain and temperature sensibilities are modified in a way similar to that found with lesions of the internal capsule. The change extends for 1 or 2 cm. over on the sound side of the body. There are astereognosis and loss of position sense.

The severe pain on the paretic side is persistent, paroxysmal and often intolerable and does not yield to drugs. It involves the whole side of the body, including the face and trunk. The pain is spontaneous or is evoked by contact with heat or especially with cold, by passive movement of the extremity or by deep pressure.

Two symptoms of the second order are sometimes observed, rectal and vesical tenesmus and hemianopia.

In two cases abnormalities of the functions of the bowel and bladder formed outstanding symptoms. The disturbances of micturition appear at the beginning of the illness. There may be retention

2. Dejerine, J., and Roussy, G.: Le syndrome thalamique, Rev. neurol. **14**: 521, 1906.

with tenesmus which is followed by frequent painful micturition. In the case just described the patient felt an imperative need to micturate, without being able to satisfy it. The tenesmus was painful, with radiation into the lower portion of the abdomen and perineum. The vesical pain persisted with marked intensity for two months. Gradually the retention disappeared, to be replaced by imperative micturition.

Vasomotor changes are marked. Early in the disease the extremities are red and congested; later they are cold and blue. The fingers are cyanotic. Trophic changes also are present in the hands and feet.

The patients sometimes have difficulty in swallowing owing to the decrease of salivary secretions and dryness of the mouth on the affected side.

Dejerine gave his pathologic material to Roussy for microscopic study, and in 1907 Roussy [3] published his famous monograph on the optic thalamus. He had performed numerous animal experiments testing the effect of artificial thalamic lesions and had carefully studied serial sections of the brains of five patients, including that of Madame Jossaume. He found that the clinical symptoms in these different cases were dependent on lesions localized in exactly the same region of the thalamus. He not only determined the precise location of the central lesion but studied the associated degeneration in the tracts.

In summing up the Jossaume case he pointed out that the clinical signs of deep and superficial anesthesia on the left, rapidly regressive hemiplegia, slight hemiataxia, astereognosis and sharp, stubborn pain on the paralyzed side corresponded anatomically with a primary lesion of the thalamus entirely destroying the posterior third of the lateral nucleus, encroaching mesially on the medial and central median nuclei, on the pulvinar behind and laterally, cutting into the posterior limb of the internal capsule and the posterior portion of the lenticular nucleus. "We believe," said Roussy, "that with the support of these findings there is now good reason to admit the existence of a new clinical syndrome produced by lesions in the optic thalamus, the thalamic syndrome."

He stated the five cardinal points of the new syndrome as follows:

1. Loss of superficial and particularly deep sensation on the side of the body opposite the lesion

2. Transient hemiplegia

3. Slight ataxia on the affected side of the body, with some astereognosis

4. Intense, stubborn pain on the affected side, not yielding to any treatment

5. Choreo-athetoid movements of the paralyzed side

3. Roussy, G.: La couche optique. Le syndrome thalamique, Paris, G. Steinheil, 1907.

Roussy finally concluded that although the sensory disturbances can be referred to thalamic loss the motor symptoms develop because in the vast majority of cases the areas of softening or of hemorrhage do not remain localized in the thalamus but invade neighboring structures, such as the internal capsule. Hemiataxia is an exception, as it was thought by Dejerine and Roussy to result from the loss of the sense of limb position and hence could be related to the thalamic lesion. Hemianopia, which is sometimes present in cases of thalamic involvement, is also a result of encroachment on the optic tract, optic radiations, optic geniculate body or perhaps, even more often, the visual projection area in the cerebral cortex.

Roussy built the syndrome on such a firm pathologic basis that subsequent work has consisted chiefly of interpretation and analysis of symptoms. Little more is now known about the thalamus than he described, but more of the thalamic connections have been worked out, more is known of the blood supply of the region and new theories of sensation have been developed.

Across the channel Henry Head read Roussy's reports and was impressed by the accounts of dysesthesia in some of the patients. Madame Jossaume showed the response of dysesthesia soon after her trouble began. Another patient could not feel pinpricks on her arms and legs well but instead felt a painful, numb sensation which was not at all localized at the point of stimulus. In one of Thomas' cases a pinprick on the finger was felt on a neighboring finger, and a prick on the ear was felt on the cheek, in some cases the point of perception being 10 cm. away from the real stimulus.

Head had vivid memories of how his own arm had felt when the superficial radial nerve was regenerating. In fact, the dysesthesia and loss of localization of the French patients with the thalamic syndrome sounded much like his own description of protopathic sensation. He had said that in the stage of protopathic sensibility the punctate end-organs have a high threshold and respond in an all or nothing manner. Sensation radiates widely and is even referred to remote areas. Localization is deficient. In addition, the pleasure-pain tone accompanying sensation is altered so that the painful sensations have a peculiar intense quality and pleasurable ones a corresponding accretion of pleasure tone. An area endowed with protopathic sensibility alone is in a state of defective sensibility; for all stimuli the threshold is high, and yet the response is peculiarly vivid, so much so that the state is commonly described as one of hyperalgesia.

Head [4] found a patient who showed Roussy's five points, with clear signs of dysesthesia. When a pin was lightly dragged across her face

4. Head, H.: Studies in Neurology, London, Hodder & Stoughton, 1920.

or trunk, she exhibited intense discomfort when the midline was passed; not only did she cry out that it hurt her more, but her face became contorted with pain. However, she insisted that, although the stimulus was more painful, it was "less plain" and "less sharp" than over normal parts. The prick was less distinct but hurt more. Head said:

> This hyperalgesia or over-reaction would seem to point to a lowered threshold to the prick of a pin. But measured stimulation with the spring algesimeter shows that if anything the threshold is a little raised; she never responded with certainty over the abnormal (left) half of her body to a stimulus which can evoke a sensation of pricking on similar normal parts to the right of the middle line, . . . the same stimulations, provided they are sufficiently strong to cause pain, produce a more uncomfortable sensation on the abnormal side.

The term overreaction is of special significance, because Head said he believed that overreaction is characteristic of certain lesions in the thalamus. The mere loss of sensation on one side of the body could be produced by interference with sensory impulses as they enter the optic thalamus or as they pass to the cortex by way of the internal capsule. Complete destruction of the thalamus would result in hemianesthesia, but then there would be neither spontaneous pain nor the overreaction.

In these cases of overreaction Head found that pressure is particularly liable to produce distress and increased reaction on the affected side. This increased reaction is frequently, though not necessarily, associated with a lowering of the threshold. When the pressure is exerted there is something terrifying about the crushing sensation, especially when a bone is pressed on. The condition is less a pain than an unbearable and distressing sensation, and in this way differs profoundly from the prick of a sharp point.

Thermal sensibility may be actually diminished so that the degrees of heat and cold belonging to the middle of the thermal scale may be appreciated as less hot or less cold than they would be on the normal side of the body. As soon as the extremes above 47 or below 26 C. are approached, the sensations experienced are those of greater heat and greater cold on the affected half of the body. The sensations are not necessarily those of excessive heat or cold, but the patient may complain of disagreeable boring or pricking sensations.

Head found also that sensations normally accompanied with a pleasurable feeling produced an overreaction. One patient could not recognize any thermal stimulation as such, and yet over the affected half of the chest large tubes containing water at from 38 to 48 C. evoked intense pleasure. This was shown not only by the expression of the woman's face but by her exclamations, "Oh! that's lovely, its so soothing, so very pleasant!" In one case a tube containing water at 38 C. when applied to the normal palm was said to be warm, but the

patient cried out with pleasure when it was placed in the affected hand. His face broke into smiles, and he said, "Oh! that's exquisite. That's real pleasant."

Head was the first to notice that in states of emotion the two sides of the body react differently in cases of thalamic involvement. Music is peculiarly liable to evoke a different reaction on the two halves of the body. One patient was unable to go to his place of worship because he could not bear the effect of the hymns on his affected side, and his son noticed that his father constantly rubbed the affected hand during the singing. A highly educated patient confessed that he had become more amorous since the attack, which had rendered the right half of his body more responsive to pleasant and unpleasant stimuli. He said: "I crave to place my right hand on the soft skin of a woman. It's my right hand that wants the consolation. I seem to crave for sympathy on my right side." Finally he said, "My right hand seems to be more artistic."

Head was convinced that protopathic sensibility for various reasons was not merely a temporary expression of regenerating sensory nerve fibers but a distinct functional entity normally held in selective control by the epicritic system. Protopathic sensibility is controlled through the thalamus; epicritic, through the cerebral cortex. The characteristic lesions producing the thalamic syndrome lie in the lateral part of the thalamus, where the thalamic radiation passes to the cortex and the corticothalamic fibers enter the thalamus. Head regarded the symptoms of overreaction and spontaneous pain as release phenomena. Whether or not one accepts Head's theories of protopathic and epicritic sensation, the idea of release phenomena has strong anatomic justification.

Head pointed out that the optic thalamus as an anatomic structure is an extremely complex portion of the brain which not only contains the terminal center for certain aspects of sensation but plays a threefold part in the fate of sensory impulses. First, it contains the termination of all secondary sensory fibers. Here the sensory impulses are grouped afresh and redistributed in two directions, to the cerebral cortex and to the gray matter of the thalamus itself. Second, it contains a mass of gray matter, the essential organ of the thalamus, which forms the center for certain fundamental aspects of sensation. It is complementary to the sensory cortex and exercises different functions in the production of sensation. Lastly, the lateral part of the thalamus is an organ through which the cortex can influence the essential thalamic centers, controlling and checking their activity.

The most remarkable feature in cases of thalamic involvement is not loss of sensation but an excessive response to affective stimuli. This may be accompanied with much or with little loss of sensation,

but the extent of this loss, according to Head, bears no relation to the amount of the overreaction to painful stimuli. It is necessary only that sufficient sensory impulses, capable of exciting discomfort, should be able to reach the consciousness.

The pains and uncomfortable paresthesia which occur in these cases have been explained by some observers as due to irritation. Now, all vascular lesions of the nervous system notoriously tend to produce the greatest disturbances of sensation at the time when they occur; the subsequent progress of the disease always shows a certain amount of recovery. But in the group of cases of thalamic involvement the pain and overreaction come on during the stage of recovery of function. They may appear a considerable period after the stroke and last unaltered for years. The response to pleasurable stimuli is also increased in some of these cases, a condition incompatible with the existence of an irritative lesion which evokes pain.

It is well known that a lesion of the cerebral motor cortex produces not only a loss of voluntary movement but also a positive effect in the increased tone of the extremities. The same condition is revealed on the sensory side in cases of thalamic disease accompanied with excessive response to peripheral stimuli. Since the paths from the cerebral cortex to the thalamus come from all parts of the cortex, the functions they exercise cannot be removed by partial destruction of the cerebral hemispheres. The only method of releasing the optic thalamus from cortical influence is to destroy the lateral nucleus, in which the majority of the corticothalamic fibers seem to end.

All the stimuli which produce an excessive effect when the thalamus is freed from cortical control contain elements which can excite the essential center of this organ. The nearer a sensation approaches pure discomfort, the more certainly will the response be exaggerated on the affected side of the body. States of pleasure and stimuli such as warmth also may evoke excessive manifestations on the abnormal side. The activity of the essential thalamic center is mainly occupied with the affective side of the sensation. The feeling tone of somatic or visceral sensation is the product of thalamic activity. Since most stimuli which act on the body in daily life are noxious and contain a disagreeable element, most sensations experienced by a patient with a lesion of the optic thalamus are painful.

Holmes and Head [5] (1911) stressed the development of deafness in a certain number of cases of the thalamic syndrome. The deafness was usually bilateral but greater on the affected side of the body. They described a case of their own in which deafness was a symptom and

5. Holmes, G., and Head, H.: A Case of Lesion of the Optic Thalamus with Autopsy, Brain **34**:225, 1911.

found reports of four others in the literature. There is sometimes associated an extreme susceptibility to loud sounds, which may actually become painful to the patient.

Earlier workers on the problem of the thalamic syndrome gave little attention to the motor side. Roussy and his immediate followers felt that the motor symptoms resulted from involvement of neighboring motor tracts rather than from the thalamic lesion itself. By 1925, when Hillemand [6] published his thesis on the thalamic syndrome, the motor disturbances were given as much emphasis as the sensory disturbances.

The motor symptoms which are found in cases of the thalamic syndrome may be grouped for purposes of discussion under the three headings ataxia, contractures and abnormal movements. This leaves out of consideration the hemiparesis which is due to the spread of the lesion into the internal capsule or involvement of the cerebral peduncles. We wish to trace for a moment the different views in respect to these three motor abnormalities and their interrelations.

The first paper describing the thalamic syndrome, by Dejerine and Egger in 1903, laid stress on the motor incoordination. In fact, it was entitled "A Contribution to the Study of the Pathologic Physiology of Motor Incoordination: Ataxia of Peripheral Origin and Ataxia of Central Origin." The ataxia in the case of Madame Jossaume appeared to them to be the feature of her illness of greatest interest and significance. In this case they noticed decomposition of movement or asynergia. There was ataxia in the finger to nose test, associated with a tremulousness of movement. Dejerine compared the ataxia with that found in patients with tabes who had completely lost deep sensation in the arms. He observed that the tabetic ataxia was much more marked than that found in the patients with the thalamic syndrome. Deep sensation was greatly impaired in both cases. The difference lay, he believed, in the location of the lesion. In tabes the fibers mediating deep sensation are injured at the point where they enter the cord. Under these conditions they establish no reflex connections in the nervous system. In the thalamic syndrome only those fibers are injured which are destined to mediate conscious information concerning the position of the extremities. The proprioceptive pathways connecting with the brain stem and cerebellum, which control the postural reflex, are intact.

Later it became clear that many of the symptoms of ataxia seen in these patients are similar to those commonly related to cerebellar lesions. In many cases a diminution in tone can be demonstrated in

6. Hillemand, P.: Contribution à l'étude des syndrômes de la région thalamique, Paris, Jouve & Cie, 1925.

the extremities, as well as intention tremor, ataxia and asynergia. The large efferent pathway from the cerebellum lies in the superior cerebellar peduncle. Many of these fibers end around cells in the red nucleus, but at least a third of the pathway passes forward to end in the thalamus. A lesion in the realm of the posterior cerebral artery may injure the fibers from the cerebellum to the thalamus. This may be a part of the typical thalamic syndrome. By means of perforating branches the posterior cerebral artery supplies also the capsule and cells of the red nucleus as far caudad as the oculomotor nucleus. A large proportion of the fibers of the cerebello-efferent system may thus be injured.

It appears then that at least two factors may operate in the production of ataxia. There may be loss of conscious information concerning the position of the extremities owing to injury of the proprioceptive pathway to the thalamus. The large pathway carrying impulses from the cerebellum to the thalamus or to the red nucleus may be involved.

Abnormal movements are usually observed in the extremities. It is difficult to classify abnormal movements, and those associated with the thalamic syndrome are of various types. Intention tremor often appears in the hand in the performance of the finger to nose test. The intention tremor is probably related to the injury of the cerebellar pathways.

Other patients show movements of the choreo-athetoid type. There is no adequate information concerning the lesions in the nervous system which produce this type of movement. Many investigators feel that these lesions are related to the basal ganglions or their projection systems. It is clear that after lesions of the subthalamic nucleus of Luys, unilateral abnormal movements of the extremities appear on the side of the body opposite the injury. They are choreo-athetoid in type. This condition is known as hemiballism. The premamillary and postmamillary branches of the posterior cerebral artery penetrate and supply a large portion of the subthalamic region. It may be involvement of this area which produces the choreo-athetoid movements. The movements may also in part be dependent on the loss of information concerning the position of the extremities.

The abnormal movements of the hand are exaggerated by changes in position or by exertion. They are increased also by activity of the other hand. In certain cases the abnormal hand tends to duplicate all the movements of the normal one. Thus, the abnormal hand may endeavor to help with fastening buttons and tying shoelaces and show all the movements of the normal hand, even though it is not intentionally used in the activity. In walking the hand is often extended

behind the body, with the arm in maximal internal rotation so that the palm turns backward.

The contracture seen in cases of the thalamic syndrome is entirely different from that encountered in hemiplegia. It is an active living contracture which varies in intensity from day to day and increases with voluntary movement.

Hillemand said that by means of the contracture it is usually possible to recognize cases of the thalamic syndrome. The upper extremity is much more involved than the lower. There is strong flexion at the elbow, and the wrist is slightly flexed and pronated. The hand is rarely closed. The fingers are straight. Often the metacarpophalangeal joint is moderately flexed, while the second and third phalanges are completely extended. There may be unusual adduction of the fingers so that they overlap. Sometimes the fingers are hyperextended at all joints, as in congenital athetosis. Vasomotor and trophic changes are marked in the hand. Indeed, the French authors speak of the "thalamic hand" as characteristic of the syndrome.

Although the arm appears to be in strong contracture, passive movement can be carried out easily, and the contracture seems to melt away. Movements are difficult because of poor coordination between the prime movers, synergist and antagonist muscles. The intention contracture, according to Hillemand, plays a large part in the production of the athetoid movement.

In summary, it is seen that the motor abnormalities are dependent on several possible factors. Owing to the incompleteness of knowledge of the physiology of abnormal movements in general, it is impossible at present to make a complete analysis. Moreover, the movements show a great variation in different cases of the thalamic syndrome dependent on the extent of the anatomic involvement. The two most important factors are the involvement of the efferent fibers of the cerebellum and the loss of information concerning the position of the extremities. These two abnormalities are present in all typical cases of the thalamic syndrome in which choreo-athetoid movements form a cardinal symptom. A third factor in the production of abnormal movements is the involvement of the area of the subthalamus by occlusion of perforating branches of the posterior cerebral artery. This subthalamic injury is inconstant and hence accessory to the typical picture.

The importance of the vasomotor and trophic changes in the thalamic syndrome has not been sufficiently emphasized. Although the pain may be late in appearance, a case of the thalamic syndrome may be recognized early by the unusual vasomotor changes on the paralyzed side. There is great swelling of the extremities, which are warm to the

touch. This may persist for weeks and then disappear. The skin remains thin and shiny. Scaling of the epidermis appears in the region of the hand, and trophic changes are noted in the nails. It is difficult to understand the mechanism of the vasomotor change. Is the reflex arc controlling the tone of the smooth muscle of the vessel walls injured on its sensory side? Or is there some injury of a local mechanism in the region of the thalamus controlling the smooth muscle of the blood vessels?

It must always be remembered that the pain may appear to be localized in the abdominal viscera. We have seen recently a patient with thalamic pain who experienced severe discomfort in the upper portion of the abdomen, interpreted as due to a gastric ulcer. No abnormalities in the intestinal tract or in the abdominal cavity were observed at operation or at subsequent postmortem examination.

In several cases of the thalamic syndrome we have noticed that the pupils were of unequal sizes. The smaller pupil is found on the same side as the lesion in the brain; the larger, on the affected side of the body. The smaller pupil is the abnormal one. There is a pathway from the hypothalamus which controls the sympathetic innervation of the pupils and is uncrossed. After injury to this pathway the pupil becomes smaller on the side of the lesion.

The whole subject of the thalamic syndrome became confused in the years which followed the publication of Dejerine's first article. Hardly a volume of the *Revue neurologique* was published without two or three articles referring to the thalamic syndrome. Patients were described with various degrees of sensory involvement and motor disturbances. A subthalamic syndrome was formulated. It remained for Foix and Masson [7] (1923) and Foix and Hillemand [8] (1925) to clarify the whole subject by pointing out the relationship between the physiologic disturbances and the vascular lesions. Since the vascular involvement has to do almost entirely with the posterior cerebral artery, Hillemand described the syndrome of the posterior cerebral artery. He studied carefully the branches of the artery and their relationship to the anatomic structures. The abnormalities seen in these patients become understandable when the anatomy and physiology of the portions of the brain supplied by the different branches of the posterior cerebral artery are considered.

While thrombosis of the posterior cerebral artery is less common than thrombosis of the middle cerebral, it occurs frequently. The

7. Foix, C., and Masson, A.: Le syndrome de l'artère cérèbrale postérieure, Presse méd. **31**:361, 1923.

8. Foix, C., and Hillemand, P.: Les syndromes de la région thalamique, Presse méd. **33**:113. 1925.

complexity of the area supplied explains its clinical interest. It gives branches to the peduncular region, the subthalamic and thalamic areas, the visual projection area in the cerebral cortex, the splenium of the corpus callosum and the inferior and mesial surfaces of the temporal lobe. The posterior choroid artery supplies large areas adjacent to the lateral ventricles.

This great number of branches explains the possibility of many symptoms which form part of a great syndrome. One sees it from time to time completely realized. It is important to understand that thrombosis of a single branch of one of the great cerebral arteries seldom occurs without some impairment of nutrition throughout the whole course of the artery. Any sclerotic process involves the artery as a whole. Sclerotic patches appear in its walls at the base of the brain. They encroach on the lumen of the vessels, decreasing the flow of blood to the whole area which it supplies. Smaller branches may become completely occluded, giving rise to focal symptoms. Other neighboring areas suffer from impairment of circulation.

This explains the symptoms often associated with the thalamic syndrome. There is seldom a completely isolated lesion of the thalamus, subthalamus, calcarine area or inferior surface of the brain. Instead, there are multiple foci of softening dependent on the breaking down of nerve tissue due to loss of nutrition. This gives diverse symptoms owing to involvement of gray and white matter. If symptoms of one type predominate and appear in frequent association, they form the background of the whole picture. This is true of the thalamic syndrome. The vascular lesion may occur in the trunk of origin of the posterior cerebral artery, during its course or in any of the branches. Certain branches supply areas which are so important that a minute lesion gives rise to grave symptoms.

The artery arises from a bifurcation of the basilar trunk, encircles the cerebral peduncle and travels to the level of the optic colliculi. It then crosses to the temporal lobe, where it lies on the internal border of its inferior face and divides into three terminal branches. The anterior branch by a recurrent path turns to the anterior pole of the temporal lobe. The postero-external branch travels over the inferior surface of the temporo-occipital lobe, supplying the fusiform lobule and the last external temporal convolution. The postero-internal branch is the artery to the calcarine area. It lies buried in the calcarine fissure. This branch supplies the internal face of the temporal lobe. It seems to be a continuation of the main trunk. In summary, the anterior or anterior temporal branch supplies the anterior part of the inferior temporal gyrus, hippocampal gyrus and occipitotemporal gyrus. The postero-external or posterotemporal branch supplies the posterior part

of the inferior temporal, hippocampal and occipitotemporal gyri and also the anterior part of the lingual gyrus. The calcarine portion of the postero-internal branch supplies the posterior part of the lingual gyrus and the inferior half of the cuneus. It also sends blood to the quadrate lobe and the splenium of the corpus callosum.

The posterior cerebral artery is seldom occluded at its origin. There is an anastomosis by means of the posterior communicating arteries with the circle of Willis. This connection is of variable importance. Sometimes the posterior communicating artery is a large trunk. There is also considerable anastomosis with neighboring arteries in the peripheral area. Softening in the region of the posterior cerebral artery is usually subtotal. The peduncular area tends to be excluded.

The blood supply of the brain stem at the level of the cerebral peduncles, according to Foix and Hillemand, simulates the same general pattern seen at lower levels in the medulla (fig. 1 *A*). There are branches to midline structures, short circumflex and long circumflex arteries. Thus, in the medulla there are short branches entering the midventral area and supplying structures on each side of the midline as far dorsal as the fourth ventricle or the aqueduct of Sylvius. The short circumflex branches supply a more lateral portion of the brain stem. The long circumflex branches in the medulla are the cerebellar arteries. They supply the most lateral portion of the brain stem.

In the peduncular region the quadrigeminal bodies simulate the long circumflex arteries (fig. 1 *A*). They arise from the posterior cerebral artery before its anastomosis with the posterior communicating artery. Each quadrigeminal artery bifurcates into two branches, one to the optic and one to the acoustic colliculus.

The posterior choroid artery may arise separately from the posterior cerebral artery or by a common trunk with the quadrigeminal artery (fig. 1 *A*). The posterior choroid artery gives off six or seven rami to the cerebral peduncles and afterward several short circumflex branches. There are several branches to the anterior part of the optic colliculi and one or two to the geniculate bodies. The posterior choroid artery also gives off one or two twigs to the splenium of the corpus callosum. Other branches from the posterior choroid artery are given off to the splenium from the lateral ventricle.

The main trunk of the posterior cerebral artery surrounds the cerebral peduncle and gives off several circumflex branches. The anterior choroid artery from the internal carotid artery swings backward and also gives off branches to the base of the peduncle.

The short, or paramedian, branches of the posterior cerebral artery have been described best by Hillemand. He divides them into two groups, depending on whether they are given off in front of or behind

the mamillary bodies (fig. 1 *B*). Although the manner of origin of these branches shows considerable variation, the area supplied by them is constant.

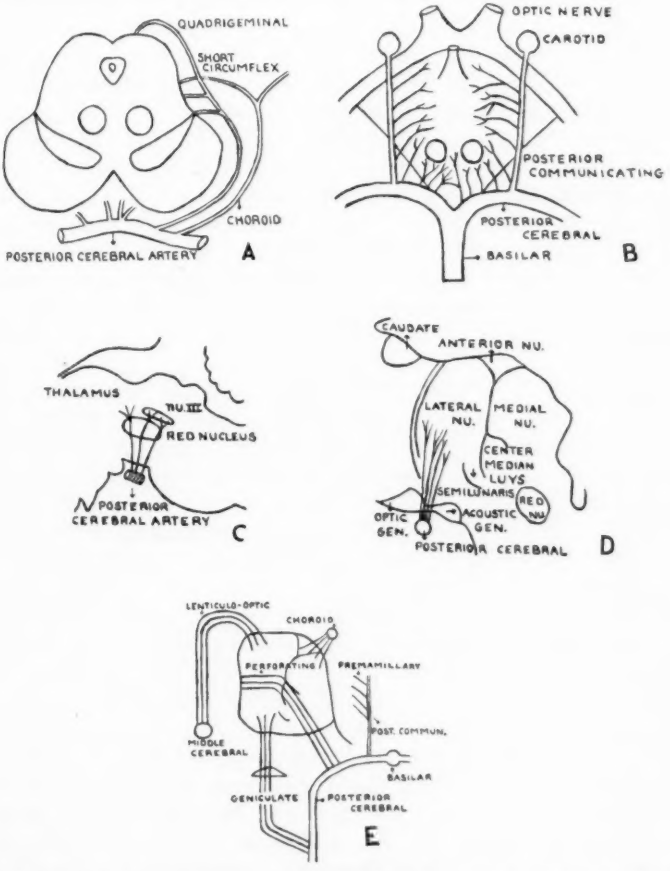

Fig. 1.—*A*, the blood supply of the region of the cerebral peduncles, showing the origin of the quadrigeminal and posterior choroid arteries from the posterior cerebral artery. The pattern of the blood supply to the brain stem is clearly shown. It consists of small branches supplying the midline structures, short circumflex and long circumflex branches. *B*, the premamillary and retromamillary arteries are given off from the posterior communicating and posterior cerebral arteries. *C*, the inferior group of retromamillary arteries given off from the posterior cerebral artery supply the anterior portion of the capsule of the red nucleus and the oculomotor nucleus. *D*, the geniculate branches arising from the posterior cerebral artery supply the lateral nucleus of the thalamus. Occlusion of these branches gives rise to the thalamic syndrome. *E*, diagram showing the blood supply of the thalamus.

The premamillary branches are given off from the posterior communicating and posterior cerebral arteries (fig. 1 *B*). They are comprised of a dozen trunks of variable size. They usually arise separately at regular intervals, but in some cases they are given off from common trunks.

The retromamillary branches again form two separate groups (fig. 1 *B* and *C*). The posterior, or peduncular, branches supply the areas on both sides between the cerebral peduncles (fig. 1 *C*). They give blood to the region of the red nucleus as far caudad as the lower end of the oculomotor nucleus (fig. 1 *C*). The anterior group supply the subthalamus and a portion of the thalamus itself (fig. 1 *B*); they may be called the thalamoperforating arteries. Sometimes they are given off from a common trunk, but there are usually at least a dozen branches. They give blood to Forel's field and the retrothalamic groups of fibers. The thalamoperforating branches also supply a portion of the external nucleus of the thalamus as far as its lateral surface (fig. 1 *E*).

The geniculate arteries are the most important branches of the posterior cerebral artery, as their occlusion gives rise to the typical thalamic syndrome (fig. 1 *D* and *E*). They are given off at the point where the artery crosses from the brain stem to the inferior surface of the temporal lobe. There are five or six of these small arteries, usually arising separately. They penetrate the optic geniculate body vertically and supply the posterolateral part of the external nucleus of the thalamus, the antero-inferior part of the pulvinar, the internal part of the optic geniculate body and the external part of the acoustic geniculate body. They also supply the posterior portion of the internal capsule.

There remains but to describe the distribution of the posterior cerebral artery on the surface of the hemisphere (fig. 2). It supplies all the inferior surface of the cortex and the inferior surface of the temporo-occipital area except for the anterior tip, which is supplied by the middle cerebral artery (fig. 2 *A*). The area of the posterior cerebral artery extends on the external face of the hemisphere over the third and sometimes the second temporal convolution (fig. 2 B). It supplies all the calcarine area, the mesial surface of the temporal lobe, part of the hippocampal gyrus and the splenium of the corpus callosum (fig. 2 *C*).

The symptoms produced by occlusion of the cortical branches may be summarized briefly. There are two symptoms, hemianopia and alexia. Hemianopia is dependent on the destruction of the visual projection area around the calcarine fissure. In many cases of the thalamic syndrome the hemianopia is quadrantic, involving especially the upper quadrant. Most investigators believe that hemianopia, when

present in cases of the thalamic lesion, is dependent on destruction of the calcarine area rather than of the optic tract, geniculate body or optic projection system. Aphasia, which is an almost pure alexia, is seen when the lesion occurs on the left side in right-handed persons. This is dependent on damage to the fibers in the splenium of the corpus callosum.

The relation of the choroid arteries to the thalamus is of considerable interest. Not only do they irrigate a large part of the dorsolateral portion of the thalamus, but perforating branches from the anterior choroid artery penetrate the hypothalamus from below and may supply a ventrolateral portion of the lateral thalamic nucleus. In

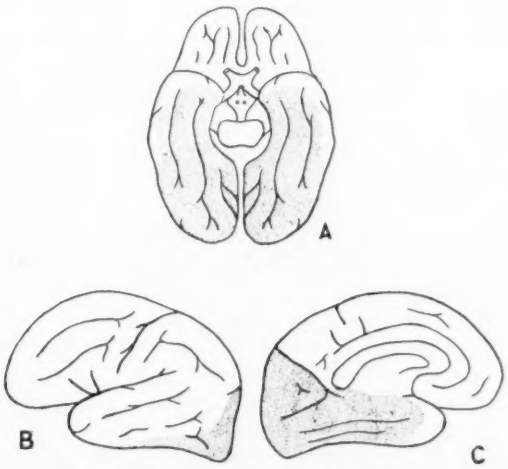

Fig. 2.—*A*, distribution of the posterior cerebral artery on the inferior surface of the brain. *B*, distribution of the posterior cerebral artery on the lateral surface of the brain. *C*, distribution of the posterior cerebral artery on the mesial surface of the brain, including the calcarine area.

their course over the dorsal surface of the thalamus the anterior and posterior choroid arteries lie in close approximation.

There are two posterior choroid arteries. They may arise separately or as a common trunk at the point where the posterior cerebral artery gives off the peduncular arteries. The principal choroid artery surrounds the peduncle, giving off six or seven branches to the cerebral peduncle. It also supplies some short circumflex branches. Other branches go to the anterior part of the optic colliculus and one or two to the corpus callosum, and then the main trunk irrigates the choroid plexus.

The accessory posterior choroid artery has a more limited territory. It runs to the lateral ventricle. There is a balance between the importance of these two posterior arteries.

The anterior choroid artery comes from far in front. It is situated first in front of and then outside the curve of the posterior cerebral artery. It turns dorsad over the cerebral peduncle, to which it furnishes numerous branches.

The anterior and posterior choroid arteries above the cerebral peduncle run almost parallel. The anterior is slightly above the posterior artery. They furnish branches to the posterior horn of the lateral ventricle and then describe a circle with the concavity anteriorly. At the point where this circle begins, a number of branches are given off to the posterior part of the pulvinar. The importance of these small branches merits the name of the pedicle of the pulvinar. They supply the postero-internal portion of the nucleus.

The anterior and posterior choroid arteries run over the superior and internal border of the thalamus in contact with the choroid plexus. A number of branches are given off to the thalamus which enter the superior surface.

With this survey of the branches of the posterior cerebral artery, it is best to turn next to the thalamus and consider with Hillemand its complex blood supply (fig. 1 *E*). It may be divided into five sources: (1) premamillary branches; (2) retromamillary branches, especially thalamoperforating; (3) geniculate arteries; (4) the posterior choroid artery from the posterior cerebral artery and the anterior choroid artery from the internal carotid artery, and (5) the lenticulo-optic artery from the middle cerebral artery.

The premamillary branches, like the retromamillary and geniculate arteries, are extremely small (fig. 1 B). The most anterior of the premamillary arteries arise from the posterior communicating arteries and the caudal three or four from the posterior cerebral artery. They supply the anteroventral portion of the thalamus in its mesial portion.

The thalamoperforating branches of the retromamillary group supply the posteromedial portion of the thalamus and also a part of the external nucleus (fig. 1 *B* and *E*).

The geniculate branches supply the postero-inferior portion of the external nucleus (fig. 1 *D* and *E*). This area usually includes the part of the ventrolateral nuclei in which sensory projection fibers end, the semilunar nucleus and part of the central medial nucleus of Luys. They also supply the area where fibers from the cerebellum terminate. The area of this artery also includes a portion of the anterior end of the pulvinar and a portion of the geniculate body. The area of destruction appears larger in sections stained for cells than in those stained for myelin sheaths.

The anterior and posterior choroid arteries run in an almost parallel direction over the lateral surface of the thalamus and supply the upper and medial surface. They give off branches at intervals which plunge beneath the surface (fig. 1 *E*). Large branches are given off to the pulvinar.

The lenticulo-optic artery, a branch of the middle cerebral artery, is said to be inconstant. It supplies the anterosuperior portion of the thalamus (fig. 1 *E*).

Hillemand gave the following orientation concerning these five sources of blood supply in relation to the thalamus: A transverse section of the brain at the level of the mamillary bodies divides the thalamus into two blocks. In the anterior block the mesial portion is supplied by the premamillary branches and the lateral by the lenticulo-optic artery. In the posterior block the infero-internal portion is supplied by the thalamic perforating branches, the lateral inferior portion by the geniculate branches and the superior surface by the choroid branches.

When a horizontal section is cut through the central gray commissure which divides the thalamus into upper and lower portions, it is seen that the internal part of the superior block is supplied by the choroid artery and the external part by the lenticulo-optic artery. The internal part of the lower block is supplied by thalamoperforating branches and the external part by the geniculate branches.

Finally, when a sagittal section of the thalamus is made through the optic geniculate body, the anterior portion of the medial section is seen to be supplied by premamillary branches, the major part by thalamoperforating arteries and a small upper portion by the choroid branches. In the case of the outer block the anterior portion is supplied by the lenticulo-optic branches, an intermediate area by the thalamic perforating branches and the posterior area by the geniculate arteries.

The different nuclei of the thalamus may be considered separately in regard to their blood supply. The external nucleus is supplied in its posterior part by the geniculate artery. This usually includes the central medial nucleus of Luys and the semilunar nucleus of Flechsig. The lenticulo-optic branch supplies the anterior portion of the external nucleus, and the thalamic perforating arteries go to an intermediate portion. The anterior nucleus is in the territory of the lenticulo-optic artery. The pulvinar receives most of its blood supply from the choroid arteries, except for the antero-inferior portion, which is supplied by the geniculate arteries. The medial nucleus receives blood from the premamillary and postmamillary branches. The habenula lies within the choroid supply.

Although there are five sources of blood supply to the thalamus, the symptoms of occlusion of only two of these five sets of arteries are at present recognized. Thus, there are the syndrome of the geniculate arteries, or the true thalamic syndrome, and the syndrome of the retromamillary or thalamoperforating branches. There may be combinations of the two. Added lesions of other branches of the posterior cerebral artery may give rise to associated symptoms, such as hemianopia or alexia.

With occlusion of the geniculate arteries producing the thalamic syndrome, the position of the lesion is always the same, although its extent is variable, giving rise to marked differences in the picture. The amount of the objective sensory changes and the degree of pain are in inverse proportion to each other. The pain is marked when the objective changes are slight and vice versa. The degree of objective sensory change depends on the degree of involvement of the central nucleus of Luys and nucleus semilunaris of Flechsig, where the sensory projection fibers end. The ataxia is dependent on the loss of deep sensation and also on destruction of the cerebellar fibers to the thalamus. The choreo-athetoid movements and voluntary contracture are related to the same factors. Hillemand related the vasomotor changes to injury of autonomic centers lying below the thalamus. He postulated that occlusion of the premamillary branches supplying the anterior nucleus of the thalamus would give rise to marked autonomic disturbances.

The second thalamic syndrome is dependent on involvement of the retromamillary branches, including the peduncular and thalamoperforating arteries. The predominant symptoms are incoordination and intention tremor. The red nucleus may be primarily involved or only the cerebellar fibers destined for the thalamus. Choreo-athetoid movements and sensory changes are inconstant. The anesthesia is dependent on involvement of the sensory pathway to the thalamus.

While a large part of the subthalamic region is supplied by perforating branches from the posterior cerebral artery, it must be realized that the lateral portion is supplied by the anterior choroid artery. There is some overlap of these two sources of blood. The subthalamic nucleus is usually supplied by branches both from the posterior cerebral and from the anterior choroid artery.

The French authors give little information concerning the midbrain syndromes produced by occlusion of the branches of the posterior cerebral artery. They divide them into the syndrome of the lower portion of the red nucleus and that of the upper portion of the red nucleus. The syndrome of the lower portion includes paralysis

of the oculomotor innervation in whole or in part. In both types there are signs of cerebellar ataxia.

In most cases the lesion in the thalamus is of the nature of encephalomalacia related to thrombosis of the geniculate arteries. Certain authors have reported tumors in the thalamus which gave rise to the syndrome. Baudouin, Lhermitte and Lereboullet[9] (1930) said they felt that hemorrhage into the thalamus is more common than has generally been supposed. There are certain clinical findings that tend to differentiate hemorrhage from thrombosis. Hemorrhage into the thalamus is likely to produce severe hemiplegia which regresses, leaving the sensory abnormalities predominant. When severe pain comes on at once after the vascular injury, hemorrhage has usually been the cause. The pain developing with encephalomalacia may not appear for weeks or months after the stroke. In many cases the hemorrhage breaks into the ventricular system, and blood appears in the spinal fluid. The bleeding is more widely destructive and is likely to produce a full blown thalamic syndrome.

In cases of the thalamic syndrome the pain is known as "central pain." It is dependent on an actual lesion of the central nervous system rather than any peripheral injury.

Roussy pointed out that there are two types of pain associated with hemiparesis: The first is pain of peripheral origin, which is found in cases of marked hemiplegia with contractures. Months or years after the onset, pain may occur in the extremities, especially around large joints. This pain is not continuous but tends to occur in crises produced by fatigue, traumatism or change in atmospheric conditions. It is of the nature of rheumatic pain. It is increased by movement, calmed by repose and helped by drugs. The central pain of the thalamic syndrome involves the whole side of the body. It has no exact localization. Sometimes it is largely superficial; at other times it is a deep pain. It is usually continuous but has exacerbations. Walking often makes the pain worse, so that the patient is incapacitated. It is also made worse when the skin is touched with the finger, by deep pressure and particularly by cold. It resembles in some ways a superficial or deep burn. Warmth is the only peripheral stimulus which may give a pleasant sensation. The pain may occur in the viscera, for example, in the bladder and rectum.

Head said he believed the central pain is due to the freeing of the thalamus from control of the cerebral cortex. There has been considerable discussion as to whether central pain can occur after injury of sensory pathways at lower levels than the thalamus.

9. Baudouin, A.; Lhermitte, J., and Lereboullet, J.: Une observation anatomo-clinique d'hémorragie du thalamus, Rev. neurol. **2**:102, 1930.

The thalamic syndrome is of extreme interest both from a physiologic and from a clinical point of view. Only in rare cases is the total picture present, but partial manifestations, particularly those of central pain, are observed in many patients with vascular lesions of the brain. This is related to the fact that so many arteries supply blood to the thalamic nuclei.

PULSATIONS OF THE WALL OF THE CHEST

I. GENERAL CONSIDERATION

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The earlier clinicians, not having elaborate apparatus and complicated laboratory methods at their disposal, attempted to find signs of diagnostic value by careful observation at the bedside with the simplest clinical devices. Today these old clinical methods of examination cannot be renounced; indeed, special attention should be given to them. A large majority of physicians are not in a position to use elaborate apparatus or complicated laboratory methods at the bedside; furthermore, careful clinical observations—as may be demonstrated in the case of pulsatory phenomena—give important clues in diagnosis, clues such as can be brought to light by no other methods of examination, regardless of how elaborate. Following the example of the old clinicians, in my studies of diagnostically important pulsations of the wall of the chest I have made use of the simplest method, namely, careful inspection and palpation of the thoracic wall. In order that this method may lead to reliable results, it is indispensable that one learn it at the bedside and practice it intelligently.

METHOD

Palpation is done preferably with the hand slightly dorsiflexed, the base of the metacarpal bones being placed with slight pressure against the portion of the thoracic wall to be examined. A comparison with the radial pulse has proved to be advantageous in determining to which phase the pulsatory movement belongs. In comparison with the carotid pulse the radial pulse is delayed, but this is negligible in view of the fact that the pulsatory phenomena are of considerable duration; likewise, the carotid pulse is more easily accessible than the radial pulse. Determinations of the time made in this way have always been verified by graphic registrations. The correctness of the results acquired by inspection and palpation has been proved by a considerable number of postmortem examinations (25 per cent of all cases).[1] It can be shown that careful clinical observations, as previously indicated, are sufficient as a rule to determine the type of the pulsatory movement as well as the phase to which it belongs, provided there is no marked tachycardia. The graphic registration of movements of the thoracic

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Translated by Hugo Roesler, M.D., Philadelphia.

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors.

1. A total of twenty-five normal persons and one hundred and twenty-eight patients have been studied. The results of these studies are presented in my book entitled "Die Brustwandpulsationen als Symptome von Herz- und Gefässkrankheiten" (Vienna, Wilhelm Maudrich, 1933).

wall has been used mainly for control purposes and in order to demonstrate objectively the findings obtained on palpation.

The receptor for registration of the movements of the thoracic wall should not be attached directly to the wall, since this would permit only the registration of the displacement of soft tissue. Pulsatory phenomena, however, are mostly represented clinically by diffuse movements affecting ribs and soft tissues equally. The receiver, which is to be placed on the thoracic wall, must be held in position by a stationary support which is fastened preferably to the bed. The receptor (fig. 1) consists of a shallow metal disk-shaped chamber (*D*), measuring 5.5 cm. in diameter and 1 cm. in height, over which is stretched a rubber membrane (*M*), which should not be too thin. To this membrane is attached a cork plate (*K*) which is large enough to cover one intercostal space and both adjacent

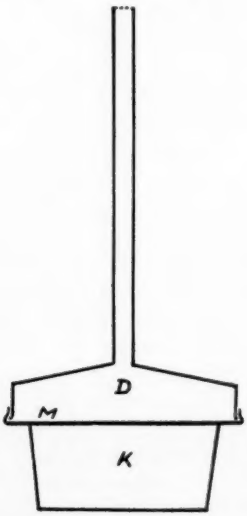

Fig. 1.—Receptor for registering the movements of the thoracic wall. *D* is the metal receiver; *M*, the rubber membrane, and *K*, the cork plate.

ribs. This cork plate rests on the portion of the wall to be examined and transmits the thoracic movements to the rubber membrane and by air transmission on a Marey tambour to a Jacquet polygraph.

PRELIMINARY PHYSIOLOGIC CONSIDERATIONS

It is necessary to recall some of the physiologic movements of the heart in order to understand pulsatory movements of the thoracic wall.

The heart undergoes a change in consistency during systole—it becomes hard and tense. In addition, its curvature is increased, as was shown by the physiologist Ludwig, by an increase in the anteroposterior and a decrease in the transverse diameters (fig. 2). The most important

and powerful movement which the heart makes during systole, is however, lever-like; it revolves on its transverse axis so that the apical portion is raised and pushes against the anterior wall of the chest. This movement is of decided importance in the formation of the apical thrust. Simultaneously with the changes in shape, the volume of the heart diminishes. This involves two processes: (1) a longitudinal shortening of the ventricular cone whereby the auriculoventricular septum moves toward the apex; (2) a centripetal marginal change, which may be distinctly recognized roentgenologically as a pulsating movement, particularly of the left margin of the heart. The latter movement is of comparatively little significance in the systolic diminution of the size of the heart. The longitudinal shortening of the ventricular cone plays the most important rôle.

The systolic change in shape of the heart and the diminution in volume are primarily responsible for the pulsations of the thoracic wall. One must not forget that these two processes have simultaneously opposing effects on the thoracic wall. The change in shape, i. e., the

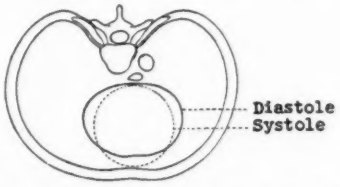

Fig. 2.—Cross-section through the heart and chest. The dash line indicates the changes in the heart during systole.

increase in curvature and particularly the rise of the apical portion during systole, causes a centrifugal movement and forces the thoracic wall outward, whereas the diminution in volume tends to draw it inward. The simultaneous effect of these two opposing forces, which may reveal differences under pathologic conditions, produces a number of pulsatory phenomena the analysis of which presents considerable difficulty. Thus, pulsatory movements which have been thoroughly investigated, such as the apical thrust, will be passed over, and only those few will be dealt with which claim special attention and interest from a diagnostic point of view. Some of them are not even mentioned in textbooks, and as to the origin of others there exist rather erroneous concepts.

SYSTOLIC PULSATION IN THE REGION OF THE RIGHT VENTRICLE

Under normal conditions the thoracic wall in the region of the right ventricle, i. e., the lower third of the sternum and the fourth and fifth intercostal spaces as far as the left parasternal line, usually shows no pulsation, for the two opposing systolic forces equalize each other. Not

uncommonly, particularly in a young person with an elastic thoracic wall, a slight systolic depression may be seen in the region of the right ventricle when the aspiratory force of systole (reduction of ventricular volume during systolic efflux) predominates. Mackenzie,[2] who found this depression in his graphs of the pulsations of the thoracic wall, concluded erroneously that the systole of the pathologically enlarged right ventricle always induces a depression of the thoracic wall, and this opinion is still included frequently in textbooks. The exact opposite is correct, as can easily be seen in instances of mitral stenosis. The enlargement of the right ventricle is primarily laterad, since the inflexible thoracic wall in front and the firm dorsal portion of the pericardium offer considerable resistance to dilatation in an anteroposterior direction. Hence, the heart is flattened, the base taking the form of a transverse ellipse. During systole the elliptic cross-section of the heart becomes more spherical, as shown by Ludwig, and the anteroposterior diameter increases (fig. 2). The result is a large systolic bulging of the anterior portion of the wall of the chest in the region of the right ventricle; this is palpable and often visible. This sign is predominantly found in patients with advanced mitral stenosis. Aside from hypertrophy and dilatation of the right ventricle, the dilatation of the left auricle is of importance, for it presses the heart against the anterior portion of the thoracic wall and thus furthers the development of the systolic bulging.

A. G. was a man aged 32. The postmortem diagnosis was mitral regurgitation and stenosis, with hypertrophy and dilatation of both ventricles and auricles. Clinically there was diffuse bulging in the cardiac area. The apical thrust was considerably widened, heaving and resistant, reaching to the anterior axillary line in the sixth intercostal space. The whole precordial area was lifted during systole (fig. 3), and this was more marked from the fourth to the sixth intercostal space between the sternum and the left parasternal line. The systolic bulge extended caudad to the costal arch at the left of the nipple line. At the right it reached 1 inch (2.5 cm.) beyond the right sternal border. Percussion revealed absolute flatness over the lower sternal portion caudad from the fourth rib. The cardiac dulness extended in the fifth intercostal space 2 inches (5 cm.) beyond the right sternal border. To the left of the sternum and in the left intercostal space there was an area of flatness 3 inches (7.5 cm.) in width. Auscultation revealed over the apical area a long, loud systolic and a short, rough diastolic murmur. At the base over the aorta there was a weak first sound, scarcely audible. There were similar auscultatory findings over the pulmonary artery; in addition, the pulmonic second sound was fairly loud. Roentgenograms showed a large silhouette of mitral configuration, with marked enlargement of the left auricle, which when projected on the anterior wall of the chest extended from the fourth rib to the xiphoid process.

2. Mackenzie, J.: Lehrbuch der Herzkrankheiten, German translation by C. J. Rothberger, Berlin, Julius Springer, 1923.

The systolic lift of the precordial area should be regarded as a prognostically unfavorable sign, for it is never demonstrated in the presence of mitral stenosis of slight degree. The appearance of this sign requires the presence of considerable enlargement of the right ventricle, indicating a valvular defect of higher degree and inadequate compensation. Clinically demonstrable dilatations are usually to be regarded as myogenic, i. e., distentions due to muscular failure (Romberg [3]).

SYSTOLIC DEPRESSIONS OF THE THORACIC WALL

The systolic depressions of the thoracic wall are of importance in the diagnosis of certain diseases of the heart provided they are diffuse, spreading over several intercostal spaces, and affect both ribs and soft tissues.

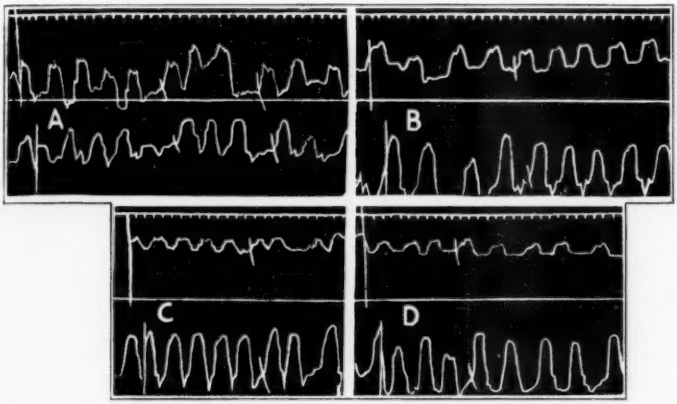

Fig. 3.—Graphs illustrating the pulsatory propulsion of the cardiac area in the presence of a high grade lesion of the mitral valve (proved at postmortem examination). The lower graph represents the apical thrust. The upper graph shows the propulsion at: *A*, the left parasternal line at the fourth intercostal space; *B*, the lower sternal area; *C*, the right parasternal line at the fourth intercostal space, and *D*, the sternum at the level of the second rib.

The centripetal forces due to diminution in cardiac volume are of paramount importance for the development of systolic depressions of the thoracic wall. In raising the question as to how the centripetal forces produce these depressions, one stumbles again and again on the erroneous concept that pericardial adhesions are an indispensable prerequisite, and yet it is a fact that these depressions are encountered

3. Romberg, E.: Lehrbuch der Krankheiten des Herzens und der Blutgefässe, ed. 4, Stuttgart, F. Enke, 1925.

far more frequently in the absence than in the presence of pericardial adhesions. The fact should not be lost sight of that a systolic diminution in volume, independent of adhesions, affects the thoracic wall in two ways: First, it exerts a *direct* aspiratory effect on the wall as far as the heart touches it; second, it acts *indirectly* as suction independent of the contact of the heart with the thoracic wall, because of the fall in intrathoracic pressure due to the rapid outflow of blood from the thoracic cavity during systole.

The direct aspiratory effect of the systolic diminution in volume is seen only when the thoracic wall and the heart are in contact. According to laws of physics, that portion of the thoracic wall must follow the centripetal movement of the heart (Kiwisch [4]) even when no adhesions are present, provided no other tissue, i. e., the lung, quickly takes up this space left vacant between the heart and the thoracic wall. A systolic depression of the wall results, especially when the lungs cannot fulfil this function of buffer, from adhesions between the heart and the thoracic wall, with obliteration of the costomediastinal pleural sinus, or from compression of the bordering portion of the lungs by an equally enlarged heart. More than anything else, however, an increase in the marginal excursions of the ventricle exerts an aspiratory effect on the thoracic wall, whether the stroke volume is increased or the mechanism of systole is altered, in that the marginal movements predominate over the longitudinal shortening of the ventricular cone. A second more or less important factor in the formation of the depression is the *indirect* aspiratory action of the systolic diminution in volume; this has been pointed out by Mackenzie [2] and Lang.[5] It is due to the decrease in the intrathoracic pressure occurring during systole, when the blood flows out of the thoracic cavity. Hence a slight depression of the thoracic wall may occasionally be seen even in a healthy person. The aspiratory action on the thoracic wall is especially pronounced in certain pathologic conditions; for instance, when the stroke volume of one ventricle and the volume of blood flowing out of the thoracic cavity are increased, as is the case in tricuspid and aortic regurgitation. The abruptness of the decrease in intrathoracic pressure during systole also is important. The more rapid the outflow of blood from the thoracic cavity, the less able will the inflow of venous blood and air—the compensating factors—be to keep pace with and counteract the considerable fall in systolic intrathoracic pressure.

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4. Kiwisch von Rotterau, F.: Neue Theorie des Herzstosses, Vrtljschr. f. d. prakt. Heilk. **9**:143, 1846.

5. Lang, G.: Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, Deutsches Arch. f. klin. Med. **108**:35, 1912.

Finally it is important to know that the effect of systolic aspiration on the thoracic wall is compensated for not only by the factors just mentioned (aspiration of air and venous blood) but also by the centrifugal force of the systolic change in shape.

In summarizing, it may be said that pathologic depressions of the anterior wall of the chest are produced by three conditions: (1) increased systolic aspiration (increased aspiratory effects due to systolic diminution in cardiac volume), (2) interference with the function of the pulmonary cushion and (3) inhibition of the systolic change in shape of the heart. Often several of these factors combine to present a distinct and diffuse depression of the thoracic wall. This type of pulsation is noted in three diseases: adhesive pericarditis, tricuspid regurgitation and aortic regurgitation.

The depression of the thoracic wall which is caused by systolic aspiration has been rightly designated by Weltmann [6] as systolic depression, for in most cases these depressions of the thoracic wall are due not to an inward pull by pericardial adhesions but to the inward pressure of the wall caused by the outer atmospheric pressure, which is merely a sequela of systolic aspiration. The anterior portion of the wall is particularly affected, because it is next to the heart and more flexible than the posterior portions, which are fixed by the spine.

The effect of the direct aspiration does not extend beyond the precordial area and is more marked as a rule in the left midclavicular line, while it is scarcely perceptible in the sternal area. The effect of the indirect aspiration, however, extends beyond the cardiac area, particularly with the marked decrease of the intrathoracic pressure, and it may in exceptional cases include the dorsal portions of the left side, resulting in a depression described as Broadbent's sign.

PULSATIONS OF THE WALL OF THE CHEST CAUSED BY THE LIVER

Between the sixth rib and the costal arch the liver is in contact with the anterior wall of the chest, separated from it only by the diaphragm and the costophrenic sinus; thus it may transmit its pulsatory movements to the thoracic wall. It is an error to believe that under normal conditions the liver reveals no pulsations; even such an excellent observer as Vaquez [7] stated in his textbook that pulsatory movements can be found only when there is congestion of the liver in connection with cardiac failure. Graphic registration of the hepatic pulse in normal persons has shown that this concept is not correct.

6. Weltmann, O.: Ueber sichtbare Pulsationsphänomene in der Herzgegend, Wien. klin. Wchnschr. **42**:829 (June 20) 1929.

7. Vaquez, H.: Diseases of the Heart, translated by G. F. Laidlaw, Philadelphia, W. B. Saunders Company, 1924.

Von Kapff [8] obtained for healthy persons, by means of a mirror sphygmograph, a hepatogram showing the characteristics of a normal auricular venous pulse, consisting of an auricular and a ventricular wave, with a typical systolic depression in between.

Three factors account for the hepatic pulse: (1) the movement of the column of venous blood, explained by an increase and a decrease in the size of the organ, corresponding to the respective phases of the cardiac cycle, (2) the transmission of movements of the heart from its diaphragmatic aspect through the diaphragm to the surface of the left lobe of the liver and (3) the systolic aspiration, not only influencing the column of venous blood but causing a direct aspiratory effect on the diaphragmatic surface of the liver. The last two factors, cardiac movement and systolic aspiration, act similarly on the liver, by causing a cephalad displacement of the whole organ during systole.

In discussing hepatic pulsations one should distinguish between volumetric variations, caused primarily by the afflux and efflux of venous blood, and movements of the whole organ. Mackenzie has expressed the opinion that only the latter condition, i. e., a systolic upward shift of the liver, is observed under physiologic conditions, while a venous hepatic pulse is noted exclusively under pathologic conditions. Von Kapff, obviously influenced by Mackenzie's opinion, likewise has stated that the marked systolic depression which he found in his hepatograms is influenced by the upward shift of the liver rather than by the efflux of venous blood. The following personal observations disprove such an interpretation of the phenomena of systolic pulsation. If one places the hand over the right costal arch of a healthy person, particularly an adolescent child, one perceives the cephalad movement of the palpating hand which corresponds to a systolic depression of the caudal surface of the liver, but one notices a similar phenomenon when the hand is placed with slight pressure in front of the right wall of the chest, over the hepatic area. One then perceives definitely a systolic depression of the thoracic wall over this area. This finding cannot be explained by assuming that the liver moves cephalad during systole; both phenomena are easily interpreted by assuming that the liver diminishes in size during systole because of aspiration of venous blood into the chest.

The correctness of this concept is proved by Hitzenberger's [9] roentgenologic observations of the pulsating diaphragm. A systolic upward movement of the diaphragm was observed only along the left leaf, where the thin left lobe of the liver is almost in the direct vicinity of the heart; here the diaphragm is influenced by the systolic aspiratory

8. von Kapff, W.: Ueber die Leberpulsation: I. Der normale Leberpuls, Deutsches Arch. f. klin. Med. **149**:279, 1925.

9. Hitzenberger, K.: Das Zwerchfell im gesunden und kranken Zustand, Berlin, Julius Springer, 1927.

effect. The right leaf of the diaphragm, however, particularly in its lateral portion, showed an entirely different type of pulsation: There was a slow presystolic cephalad movement which was followed by a rapid and marked systolic amplitude in a caudal direction. The systolic movement of the diaphragm, therefore, takes place in a direction opposite to what one would expect from an upward shift of the whole liver. Indeed, Hitzenberger, has said he considers the systolic pulsations of the right diaphragmatic leaf as an expression of a direct venous hepatic pulse. There is no doubt, therefore, that the systolic depression of the ventral wall of the chest over the hepatic area, as well as the depression in the hepatogram, is caused by the systolic efflux of venous blood from the liver. The degree of pulsatory amplitudes of the thoracic wall over the hepatic area is small under normal conditions. This movement is best perceived when the subject is holding his breath. The palm of the examiner's right hand is placed with moderate pressure on the right wall of the chest near the costal arch and approximately in the nipple line, while the left hand palpates the pulse in the radial artery. A jerky systolic depression is noted which may be found as high as the level of the fifth rib, but it increases in intensity caudad toward the costal arch. Similarly, there is found a systolic depression of the abdominal wall in the epigastric area. This pulsation in the hepatic area is hardly ever missed in an adolescent child, because the chest is elastic and flexible; it is noted in different degrees in different persons.

The degree of the systolic depression in the hepatogram, as well as the degree of the palpable depression over the hepatic area, depends on two factors: (1) the diastolic and particularly the presystolic active emptying of the right auricle, which is the prerequisite for a powerful systolic influx of blood from the liver, and (2) the force of ventricular contraction, which in two ways fosters the systolic influx of venous blood into the chest. First, the pulling down of the auriculoventricular septum suddenly increases the volume of the auricle, and, second, the diminution of the volume of the ventricle (the efflux of blood from the thoracic cavity) leads to a fall in pressure. These factors act in the same way on the venous blood, causing powerful aspiration.

Under abnormal conditions these factors change, and certain anomalies are found in the hepatograms as well as in the pulsatory phenomena of the thoracic wall. The systolic depression of the venous pulse is more marked when the stroke volume of the ventricle increases, causing a greater amount of blood to leave the thoracic cavity. Von Kapff found a particularly marked descent in the hepatograms of patients with aortic regurgitation. In patients with the same valvular lesion I have found not uncommonly a particularly marked systolic depression of the thoracic wall over the hepatic area (fig. 4 *A*).

Failure of the right ventricle, with associated overdistention of the right auricle and venous congestion, of course, will counteract the formation of a typical depression in the venous pulse and occasionally may even cause a reversal of the venous pulse picture. Similar changes are observed with the appearance of auricular fibrillation; here the presystolic emptying of the auricle does not take place, and with it the most important prerequisite for the systolic afflux of venous blood disappears, particularly in the presence of failure of the right side of the heart. Hence, the influx of blood into the right auricle takes place almost exclusively during diastole and not, as under normal conditions, predominantly during systole; with marked congestion blood flows into the right auricle only at the beginning of diastole, i. e., when the relaxed

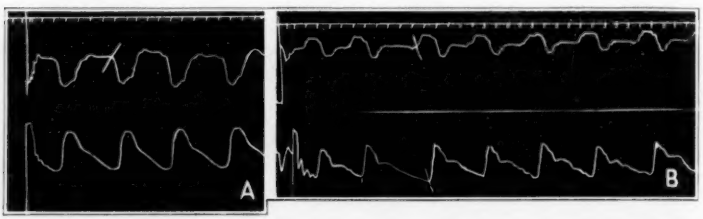

Fig. 4.—*A*, a graph of the systolic depression of the hepatic area observed in a case of aortic regurgitation of syphilitic etiology. The lower graph is for the radial artery. The upper graph was made with the receiver over the seventh and eighth ribs on the right side, 2 cm. within the anterior axillary line. The mark indicates the beginning of expulsion. *B*, a graph of the pulsatory propulsion of the hepatic area in a case of tricuspid regurgitation. The lower graph is for the radial artery. The upper graph was made with the receiver over the seventh rib in the midaxillary line on the right side.

right ventricle, after opening of the auriculoventricular valves, offers space for the venous influx. Then a ventricular hepatic pulse results with a systolic level and a more or less steep descent at the beginning of diastole.

With this type of venous hepatic pulse, the systolic ascent is caused by congestion only, and this ascent is less easily palpable than the steep diastolic descent (diastolic collapse of the liver). The findings on palpation are again different for that type of ventricular hepatic pulse which is due to regurgitation of blood from the right ventricle in the presence of tricuspid regurgitation. Its graph differs little from the graph of the pulsation due to congestion, but palpation does not demonstrate the diastolic collapse of the liver as much as the forceful systolic elevation caused by the impact of the regurgitating blood. Not only does the bulge affect the caudal portions of the right wall of the chest in a ventral direction, but commonly a definite shift from left to

right is noted (fig. 4 *B*). This is due to the fact that the right lobe of the liver is much larger than the left lobe, so that the larger amount of the regurgitating blood flows to the right side. This results in a strong impulse to the liver, which not rarely leads to a systolic shift of the whole chest, particularly the lower portions, from left to right. This finding may be so obvious that the diagnosis of tricuspid regurgitation may be made by merely inspecting the chest.

It is not possible under normal conditions to palpate elevations of the thoracic wall which would correspond to the auricular (or ventricular) wave of the hepatogram; the force of these venous pulsations, caused merely by stasis, is too small as a rule to produce a palpable change in the surface of the liver. If, however, there is an impediment to the flow of venous blood into the ventricle during auricular contraction, a presystolic lift can be palpated in the hepatic area. This is found when there is congestion in the right side of the heart, particularly in the presence of tricuspid stenosis, in which the right auricle partly throws blood back into the veins, provided it is still capable of contraction. Thus, a presystolic regurgitation pulse results, which, as compared with the pulse accompanying stasis, may be felt as a slight elevation on the surface of the liver as well as occasionally on the wall of the chest as far as it covers the liver (fig. 5); the elevation definitely precedes the radial pulse. With associated tricuspid regurgitation there is added to the presystolic regurgitation a wave of systolic regurgitation, and a double wave in the hepatic pulse results; sometimes the first (auricular) and sometimes the second (ventricular) elevation is more marked.

ASSOCIATED PULSATORY MOVEMENTS (SECONDARY PULSATIONS); PULSATIONS OF THE CHEST IN THE FRONTAL DIRECTION

It will be necessary for the understanding of the sometimes rather complicated pulsatory phenomena to consider certain pulsatory movements which are a distinct effect of those primary movements of the thoracic wall which originate at the place of the immediate, direct effect of pulsation. The chest represents a stiff elastic system. If a pulsatory force sets up a deformation in one area, movements will not be limited to this circumscribed part but will take place also at some distance from it. Such movements may be designated as secondary pulsations or associated pulsatory movements.

The type and degree of these associated pulsatory movements are influenced by several factors: the force of the primary pulsatory impact, the point and direction of impact and the elasticity and flexibility of the bony thoracic wall. Needless to say the associated movements take place in the immediate vicinity of the pulsatory impact, and they

have the same direction as have the primary pulsations. Much more important are those distant effects of pulsatory force which, in a certain sense, take place opposite to the main pulsations. A pulsatory bulge of the thoracic wall leads to a distant flattening or depression of the ribs, and vice versa. As an example of the distant effect of the primary pulsations, one may cite the flattening of the lateral portions of the ribs in association with a powerful propulsion of the midportion of the thoracic wall, as observed in hypertrophy and dilatation of the right ventricle (fig. 6*A*). In the presence of mitral lesions one frequently observes a definite inward systolic pulsatory movement of the lateral portion of the chest extending from the fifth to the eighth rib and occasionally down to the costal arch. This associated pulsatory movement is usually much more pronounced on the right side. The following explanation may be offered: The primary pulsatory propulsion of the midportion of the thoracic wall extends rather far to the left, because

Fig. 5.—*A*, a graph showing the presystolic propulsion of the hepatic area in a case of tricuspid stenosis, compared with, *B*, a graph demonstrating the pulse in the jugular vein. The lower graph in *A* shows the apical thrust. The upper graph was made with the receiver over the right costal arch in the midclavicular line. The mark corresponds to the ascent of the apical thrust. The steep ascent in the upper graph precedes the beginning of the apical thrust (presystolic-auricular wave). The upper graph in *B* shows movement of the liver as in *A*. The lower graph is for the pulsation of the jugular vein. The graphs resemble each other.

of the asymmetrical portion of the right ventricle; this counteracts to a certain degree the formation of an oppositely directed movement on the left side.

If a pulsatory force acts on one side of the chest, an associated movement of the symmetrical portion of the other side is called forth, and this, in connection with the primary pulsation, leads as a rule to a shift of the whole chest in a predominantly frontal direction. Thus a strong impulse directed at the left side to the left and ventrad, as caused by the impact of a hypertrophic left ventricle, is associated on the right side with a flattening out of the ribs, i. e., a movement to the left and dorsad (fig. 6*B*). The total pulsatory effect will be a shift of the

whole chest in a frontal direction from right to left and more marked in the more flexible caudal portions of the chest. Thus one notices occasionally in the presence of aortic regurgitation or hypertensive disease a jerky, easily visible shift to the left, expressing the increased activity of the left ventricle. As compared with the predominant frontal direction of the movement, the sagittal (dorsoventral and ventrodorsal) component is less conspicuous, but on careful observation one may notice that simultaneous with the shift of the chest to the left a kind of rotation around the long axis takes place, so that the ribs on the left side protrude while those on the right undergo depression; i. e., they move dorsad. The frontal movement from right to left (systole) is best marked in the portions adjacent to the sternum, particularly over the sternum itself.

It is easily understood that a primary propulsion on the right side leads to a shift of the whole chest from left to right. Such pulsations are sometimes noted in cases of aneurysmal enlargement of the left

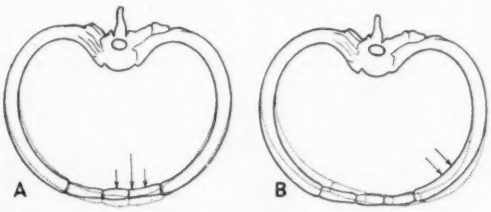

Fig. 6.—The dotted lines indicate the pulsatory shift of the thoracic wall, *A*, for a patient with a valvular lesion and hypertrophy of the right ventricle; *B*, for a patient with hypertension or a lesion of the aortic valve. The arrows indicate the direction of the primary force.

auricle, when in the presence of high grade mitral regurgitation the impact of the blood stream hits the right side of the chest. Moreover, in cases of tricuspid regurgitation the venous pulse of the liver is transmitted to the adjacent portions of the right side of the chest.

An opposite type of movement along the symmetrical portions of the contralateral part of the chest will be observed if the primary pulsatory force is not directed outward but inward, or, to express it differently, if a primary depression of the ribs takes place over half the chest. Here one will observe a propulsion of the ribs. Of this one may convince oneself by the following simple experiment: If slight pressure with the tips of the fingers is exerted against the bony thoracic wall in the region of the apical thrust, one notices simultaneously at the right side a slight propulsion and shift of the thoracic wall to the right. This roughly corresponds to those pulsations which may be observed in the patient with an adherent pericardium with systolic

depression of the cardiac area. Simultaneously with the depression of the ribs, a shift to the right is noted, and the compensation, with the movement to the right of the right half of the chest, again results in a frontal type of pulsation. This movement is hardly ever as marked as the frontal shift of the thorax in the opposite direction, as noted with increased activity of the left ventricle; this is explained by the lesser intensity of the primary force in the presence of an adherent pericardium. When the latter condition is present the systolic shift of the chest from left to right is not as marked as the jerky rebound of the thoracic wall noted during diastole.

SUMMARY

Examination by means of simple inspection and palpation is almost always sufficient to demonstrate diagnostically important pulsatory findings. The graphic registration serves merely to control the clinical findings; it should be carried out with the fixed receptor.

Pulsatory movements of the thoracic wall are essentially caused by the effect of change in shape and diminution in volume of the heart. Hypertrophy and dilatation of the right chamber in association with the dilatation of the left auricle, as encountered in cases of lesions of the mitral valve of a severe degree, lead to a forceful systolic propulsion of the precordial area near the sternum.

Systolic depressions of the thoracic wall are due to the centripetally directed movement of the cardiac systole, which exerts an aspiratory effect on the thoracic wall in two ways: (1) directly, when the heart is in contact with the thoracic wall, and (2) indirectly, owing to the fall in intrathoracic pressure caused by systole. The effect of these aspiratory forces on the thoracic wall is equalized under normal conditions mainly by two factors: (1) the oppositely directed propulsive force due to the systolic change in shape of the heart and (2) the expansion of the lungs.

Pathologic depressions of the thoracic wall during systole are due to (1) marked increase of the systolic aspiratory effect (reduction of ventricular volume during the systolic efflux), (2) inhibition of the systolic change in shape of the heart and (3) inhibition of the expansion of the lungs.

An increase of the stroke volume much more commonly causes systolic depression of the thoracic wall than do adhesions of the pericardium.

The liver may transmit its pulsatory movements to the adjacent thoracic wall. Normally the systolic efflux of venous blood from the liver often causes a depression of the portions of the thoracic wall in front of it. The systolic depression is often particularly marked in the

presence of aortic regurgitation; this is due to the increase in stroke volume and the increased aspiratory effect. Tricuspid regurgitation as a rule causes a forceful systolic propulsion of the hepatic area. The systolic impulse of the blood regurgitating into the large right lobe of the liver transmits to the whole chest a frontal movement directed from left to right. A presystolic propulsion of the thoracic wall over the hepatic area is often noted in congestive failure of the right side of the heart but particularly in the presence of tricuspid stenosis, provided the auricle is still capable of contraction.

In addition to primary pulsatory phenomena, which occur directly at the place of the pulsatory impact, secondary pulsations or associated pulsatory movements are observed. They should be looked on as distinct effects of the primary pulsatory forces. Pulsatory movements of the whole chest in a frontal direction are caused by a compensatory effect of both types of pulsations; this is observed when there is marked hypertrophy of the left ventricle, tricuspid regurgitation or mitral regurgitation, associated with aneurysmal dilatation of the left auricle to the right.

PRESENCE OF DIGITALIS IN BODY FLUIDS OF DIGITALIZED PATIENTS

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During the treatment of patients with congestive heart failure we have occasionally observed that from twenty-four to forty-eight hours after diuresis has been produced by the use of salyrgan or mercurin (the sodium salt of trimethylcyclopentane-dicarboxylic acid-methoxymercuryhydroxideallylamide) or with theophylline the patient has become ill, with nausea, vomiting, giddiness, headache and considerable weakness. In fact, in the past several years one of us has seen two patients, not alarmingly ill before such supplemental diuresis, come to rapid unexpected death in this sickness a day or two after salyrgan had been given. It is this occasional postdiuretic illness that initiated the present investigation.

There are several hypotheses that may be offered as an explanation of the symptoms that may follow diuresis induced with salyrgan. When given in the usual doses, of 1 or 2 cc., this drug may produce no diuresis, in which case the mercury may be retained in the body and cause untoward effects. However, it is not with that circumstance that we are concerned, because the illness which we are considering occurred after an output of from 2,000 to 6,000 cc. of fluid. With the elimination of such quantities of fluid, Keith and Whelan [1] have shown that 85 per cent of the mercury injected is excreted and can be recovered in the subsequent twenty-four hour specimen of urine in most instances. That, together with the common observation that repeated injections of salyrgan cause no appreciable renal damage, makes it seem unlikely that the mercury alone is the direct cause of the postdiuretic symptoms.

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1. Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation **3**:149, 1926.

A shift in the electrolytes of the body may be the explanation for such symptoms.[2] It has been found [3] that organic mercury compounds when used alone cause an increased excretion of chloride and inorganic fixed base in the urine. If the diuresis is great, there is a concomitant decrease in the chloride and an increase in the bicarbonate concentration of the serum. Blumgart, Gilligan and Volk [3e] found that alterations in the chloride and the bicarbonate content in human beings were opposite but about equal and greatest in the cases in which diuresis was the most marked. If a change in the electrolytes of the serum were to explain the symptoms, one might expect that the patient having a urinary output of 6,000 cc. or more after the administration of salyrgan would be the one to experience the ill effects. But it has been our observation that the excretion of a large quantity of fluid is not necessarily the important factor. Moreover, the studies that have been referred to showed no substantial change in the acid-base equilibrium in the blood or urine under such circumstances. Furthermore, the changes in the specific gravity of the serum and in the protein content of the blood are not constant or marked, even when the diuresis is great. Furthermore, since the publication of Keith and Whelan's studies, ammonium chloride or a similar acid-producing salt is usually given in preparation before the use of salyrgan. As pointed out by Blumgart and his co-workers, the administration of an acid-producing salt tends to obviate any great alteration in electrolytes and in the chloride and the bicarbonate concentration of the serum. Since it is with this combination of ammonium chloride and salyrgan that we have usually observed these postdiuretic symptoms, we feel that a shift in electrolytes is probably not the explanation.

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2. Since this was written an article entitled "Untoward Effects of Diuresis, with Special Reference to Mercurial Diuretics" by D. Poll and J. E. Stern has appeared (Arch. Int. Med. **58**:1087 [Dec.] 1936). They have attributed the syndrome primarily to depletion of water and chloride.

3. (*a*) Crawford, J. H., and McIntosh, J. P.: Observations on the Use of Novasurol in Edema Due to Heart Failure, J. Clin. Investigation **1**:333, 1925. (*b*) Nothmann, M.: Beobachtungen bei der Salyrgandiurese, Ztschr. f. klin. Med. **120**:158, 1932. (*c*) Fulton, M. N.; Van Auken, H. A.; Parsons, R. J., and Davenport, L. F.: The Comparative Effect of Various Diuretics in Dogs with Special Reference to the Excretion of Urine, Chloride, and Urea, J. Pharmacol. & Exper. Therap. **50**:223, 1934. (*d*) Gilligan, D. R.; Volk, M. C., and Blumgart, H. L.: Observations on the Chemical and Physical Relation Between Blood Serum and Body Fluids: I. The Nature of Edema Fluids and Evidence Regarding the Mechanism of Edema Formation, J. Clin. Investigation **13**:365, 1934. (*e*) Blumgart, H. L.; Gilligan, D. R., and Volk, M. C.: Action of Diuretic Drugs: II. Effect of Diuretic Drugs on the Acid-Base Equilibrium of the Blood in Patients with Cardiac Edema, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 191. (*f*) Keith and Whelan.[1]

An exchange of fluids in the body and relative dehydration of the tissues, occurring with marked diuresis, may be another factor in the production of such symptoms. One possibility in which this factor of relative dehydration of the tissues may play an important rôle is in the loss of fluid in and around the brain substance, causing a disturbance in the equilibrium of the dynamics of the blood and cerebrospinal fluid.

However, with the elimination of so much fluid from the body cavities and interstitial spaces through the blood stream and out through the kidneys, it seemed to us that a plausible explanation for such symptoms would be "redigitalization." In other words, if substances which act like digitalis could be found in edema fluid from the pleurae, peritoneum and leg, the transportation of that fluid through the body to the kidneys during active diuresis in a patient who is digitalized would expose the cardiovascular and nervous systems to the contained digitalis and would cause further action of the drug. The symptoms experienced by these patients would then be those of digitalis intoxication. To all clinical appearances, too, the weakness, nausea, vomiting, headache and other symptoms seem to be similar to those due to an excess of digitalis. A similar idea has been put forward by Miller and Smith,[4] but unfortunately their work has been reported only in abstract.

This hypothesis would be further validated if appreciable amounts of digitalis could be found in the body fluids of digitalized patients. Hatcher and Eggleston,[5] Cloetta[6] and Fischer[7] have found small amounts of the principles of digitalis in the urine, although earlier workers[8] had been unable to detect the excretion of these substances by the kidneys. This indicates that all digitalis is not firmly and irreversibly fixed in the body tissues.

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4. Miller, G. H., and Smith, F. H.: The Presence of Digitalis in Edema Fluid and Its Possible Clinical Significance, J. Clin. Investigation **10**:666, 1931.

5. Hatcher, R. A., and Eggleston, C.: Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, J. Pharmacol. & Exper. Therap. **12**:405, 1919.

6. Cloetta, M.: Die Darstellung und chemische Zusammensetzung der aktiven Substanzen aus den Digitalisblättern: Ihre pharmakologischen und therapeutischen Eigenschaften, Arch. f. exper. Path. u. Pharmakol. **112**:261, 1926.

7. Fischer, H.: Ueber Aufnahme, Bindung und Abbau von Digitalisstoffen und den daraus sich ergebenden Beziehungen zu ihrer Wirkung am Herzen, Arch. f. exper. Path. u. Pharmakol. **130**:111, 1928.

8. Polaillon and Carville: Etude physiologique sur les effets toxiques de l'inee, Arch. de physiol. norm. et path. **4**:523 and 680, 1871-1872. Hedbom, K.: Beiträge zur Kenntnis der Wirkungen des Antiarins, Arch. f. exper. Path. u. Pharmakol. **45**:317, 1901. Lhotak von Lhota, C.: Untersuchungen über das Verhalten der Digtalisstoffe im Körper, besonders bei der Angewöhnung an Dieselben, Arch. internat. de pharmacodyn. et de thérap. **22**:61, 1912.

METHOD

Since digitoxin is one of the most active of the digitalis glucosides and since its action and properties are better known than those of many of the other glucosides,[9] we attempted its extraction (or possibly that of digitoxigenin) from the body fluids of digitalized patients. On the basis of the medicolegal method of Schmidt,[10] modified in terms of the known physical properties of digitoxin recorded by Hatcher [11] and in the "Dispensatory of the United States," [12] we worked out a satisfactory method of extraction. Five hundred cubic centimeters or more of edema fluid from the pleurae, peritoneum or leg is acidified with a 25 per cent solution of acetic acid to a p_H of 5.2 (alcoholic methyl red being used as an indicator), which is near the iso-electric point for the precipitation of protein. To this is added an equal volume of 95 per cent alcohol, and the mixture is heated to 50 C. on a steam bath. This is filtered while hot, giving a clear to slightly yellow filtrate. This is placed in a large flask and concentrated to about 25 cc. in a vacuum at 40 to 50 C.[13] This concentrate, which is a thin gummy mass, is extracted with 150 cc. of 95 per cent alcohol and evaporated to dryness on a water bath at a temperature not higher than 45 C. This residue is dissolved in 20 cc. of 10 per cent alcohol; from 4 to 6 drops of a 35 per cent solution of ammonium hydroxide is then added to make the solution just alkaline to litmus. This is extracted three or four times with chloroform in a separatory funnel. The solution of chloroform is brought to dryness by the air bath,[14] and to this residue is added 3 cc. of chloroform and a mixture of 10 cc. of ether with 70 cc. of purified petroleum benzine in a flask. The flask is sealed with a rubber stopper and allowed to stand in the cold room for from twenty-four to forty-eight hours. The final product is a fine gray-white precipitate, which is removed by centrifugation. This is taken up in 1 or 2 cc. of Clark's solution [15] and used in the Straub preparation of the heart.

Early in the study it was learned that less than 500 cc. of fluid concentrated for digitalis substances was not productive of satisfactory results. Consequently we usually used from 1,000 to 2,000 cc. and in several instances as much as 5,000 cc. of edema fluid from the pleurae, peritoneum or leg.[16] After the precipitate was obtained by the chemical method outlined, it was suspended in from 2 to

9. Jacobs, W. A.: The Chemistry of the Cardiac Glucosides, Physiol. Rev. **13**:222, 1933. Elderfield, R. C.: The Chemistry of the Cardiac Glucosides, Chem. Rev. **17**:187, 1935.

10. Schmidt, E. A.: Ausführliches Lehrbuch der pharmazeutischen Chemie: Organisches Chemie, Braunschweig, F. Vieweg & Sohn, 1911, vol. 2, pt. 2, p. 1884.

11. Hatcher, R. A.: Some Observations on the Pharmacology of a Digitalis Body, J. A. M. A. **75**:460 (Aug. 14) 1920.

12. Wood, G. B.: The Dispensatory of the United States of America, ed. 21, Philadelphia, J. B. Lippincott Company, 1926, p. 410.

13. Because of foaming of the solution, we obtained more satisfactory results by placing the filtrate in a large evaporating dish, set into a warm room at 37 C. with an electric fan blowing over it.

14. Logan, M. A.: An Apparatus for the Evaporation of Liquids in a Test Tube, J. Biol. Chem. **86**:761, 1930.

15. Sollmann, T.: Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 786.

16. Dr. R. E. Glendy, of the Massachusetts General Hospital, furnished us with two specimens of edema fluid from the leg.

4 cc. of Clark's solution.[15] From 0.5 to 1 cc. of this was placed in a Straub preparation of the frog heart.

In all, a total of twenty-nine specimens of fluid from twenty-four patients were examined, in eighteen of which it was known that the edema accumulated while the drug was being taken. The eighteen "digitalized fluids" were specimens of edema fluid—ten from the pleurae, seven from the peritoneum and one from the leg. Two specimens of fluid—one from the pleurae and one from the leg—were examined when it was questionable whether digitalis had been taken. The remaining nine specimens—five pleural and four peritoneal—were from patients with cirrhosis of the liver, tuberculosis, neoplasm and other disorders in which it was definitely known that no digitalis had been used. These "nondigitalized fluids" were used as controls.

Male frogs of the species Rana pipiens, weighing from 20 to 40 Gm., were used for the Straub preparations of the heart. In the course of the experiments we found to some extent, but not strikingly so, the daily variation of the action of digitalis in frogs in the winter and in the spring months that has been spoken of particularly by the German writers and also by Chapman and Morrell [17] in their report on the standardization of digitalis in Canada. For the most part, the known tinctures of digitalis used as controls in our experiments from September

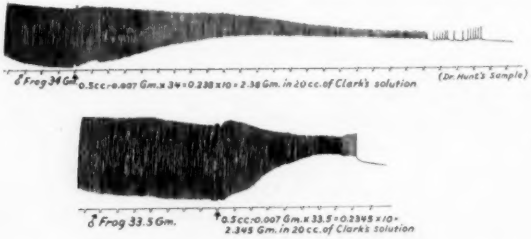
♂ Frog 34 Gm.
0.5 cc.=0.007 Gm. x 34=0.238 x 10=2.38 Gm. in 20 cc. of Clark's solution
(Dr. Hunt's Sample)
♂ Frog 33.5 Gm.
0.5 cc.=0.007 Gm. x 33.5=0.2345 x 10=
2.345 Gm. in 20 cc. of Clark's solution

Chart 1.—Two typical curves showing the digitalis effect in a Straub preparation of the heart, with systolic standstill. The dose was 0.007 Gm. of digitalis per gram of body weight. The upstroke represents systole and the downstroke diastole.

1935 to April 1936 gave uniform results. Thus, we could conclude that the curves we obtained with our "digitalized fluids" were valid.

One of the first steps in this study was to determine whether or not the chemical procedure would recover digitalis added to body fluid. Several "nondigitalized fluids" were divided into two equal portions; to one portion from 2 to 3 cc. of tincture of digitalis was added, while the other half was used as a control. In each of these trials the precipitate recovered from the fluid to which digitalis had been added, placed in a Straub preparation of the heart, showed a typical digitalis effect. No digitalis effect was obtained from the control half of the fluids.

RESULTS

Numerous experiments with the Straub preparation of the heart were performed from time to time with known strengths of fresh

17. Chapman, C. W., and Morrell, C. A.: On the Biological Assay of Digitalis and Strophanthus, J. Pharmacol. & Exper. Therap. **46**:229, 1932.

tincture of digitalis, supplied by Dr. Reid Hunt. Various strengths were used, and chart 1 illustrates two typical curves obtained from the hearts of 33.5 and 34 Gm. frogs with 0.007 Gm. of digitalis per gram of body weight, suspended in Clark's solution. When this type of curve is shown, recovery is not obtained by several washings of the heart with Clark's solution. Charts 2 to 4 *A* demonstrate a typical digitalis effect produced by concentrated edema fluid from the pleurae, peritoneum and leg, respectively, of digitalized patients. Attempts to obtain recovery of these hearts was not possible with repeated washings with Clark's solution.

Chart 5 shows the curve obtained when 1,250 cc. of peritoneal fluid was used which had been obtained from a patient with an abdominal malignant growth for whom, at the time, all the factors of digitalization were not known. Frequent paracentesis for ascites due to the ovarian malignant growth with peritoneal metastases had been carried

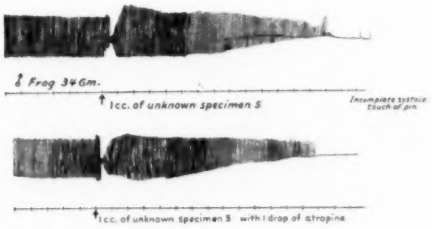

Chart 2.—The upper curve shows the effect on a Straub preparation of the heart of 1,100 cc. of concentrated pleural fluid from a digitalized patient. The lower curve shows a persistent digitalis effect, unchanged by the addition of a drop of weak solution of atropine.

out, and on one occasion when the patient was admitted to the hospital digitalis was given because of an element of myocardial insufficiency. The fluid obtained for this study was known to have accumulated after digitalization, but the patient's interval history was incoherent regarding the daily use of the drug. The fluid showed a typical digitalis effect. After the heart had come to a systolic standstill, the apex was touched with the point of a pin, which produced a more complete systole, shown at the end of the graph. This procedure, suggested to us by Dr. Hunt, gave further evidence of a digitalis effect, since it was impossible to obtain any recovery by repeated washing of the heart. At the time this abdominal fluid was obtained it was included in the group of questionably "digitalized fluids," because of the inadequate history. However, later information from relatives of the patient revealed that she had been given digitalis regularly. Therefore the patient is now included in the group of digitalized patients.

Certain of the curves suggested in places a choline effect, but it seemed unlikely from the method used that any choline might be present.[18] Several experiments in which choline was used were performed under the same conditions, but they did not yield curves like the ones we were getting. Moreover, small doses of atropine (which neither stimulate nor depress the cardiac muscle) will inhibit all the action of choline[19] but not that of digitalis.[20] Several drops of weak atropine added to the solutions tested had no influence on the type of curve obtained. Further, the presence of choline could not be detected in any of the substances under study by the chemical tests devised by Booth.[21]

In addition, it was questioned whether the curves observed could be due to the effect of calcium. Although McLean, Hastings[22] and others have pointed out the typical effect of calcium on the Straub preparation of the heart, it has been maintained by Loewi (quoted by Cloetta[23]) that the action of calcium is similar to that of digitalis, that there can be no action of digitalis without calcium and that the effects of calcium and of digitalis are to be considered as identical. However, Cloetta and Fischer[24] have shown that one can abolish a calcium effect

Chart 3.—The effect on a Straub preparation of the heart of 6,300 cc. of concentrated ascitic fluid in Clark's solution. Note the failure of recovery after washing and the complete systolic standstill.

by rinsing the heart, but not a digitalis effect; so the two are not identical. In control curves, when calcium was used, complete recovery was always obtained by washing; in no instance in which we obtained a

18. Hunt, R.: Personal communication to the authors. Hastings, A. B.: Personal communication to the authors.

19. Hunt, R.: Some Physiological Actions of the Homocholins and of Some of Their Derivatives, J. Pharmacol. & Exper. Therap. **6**:477, 1914-1915; Vasodilator Reactions, Am. J. Physiol. **45**:197 and 331, 1918.

20. Edmunds, C. W., and Gunn, J. A., in Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1928, p. 443.

21. Booth, F. J.: A Microchemical Test for Choline and Its Esters in Tissue Extracts, Biochem. J. **29**:2064, 1935.

22. McLean, F. C., and Hastings, A. B.: Biological Method for Estimation of Calcium Ion Concentration, J. Biol. Chem. **107**:337, 1934.

23. Cloetta, M.: The Biochemical Action of Digitalis, J. A. M. A. **93**:1462 (Nov. 9) 1929.

24. Fischer, H.: Beitrag zur Frage des Synergismus zwischen Digitalis- und Calciumwirkung, Arch. f. exper. Path. u. Pharmakol. **130**:194, 1928.

curve that appeared to show a digitalis effect could we abolish it by rinsing.

With thirteen of the eighteen specimens of fluid from known digitalized patients, positive evidence of a digitalis effect was obtained. Its presence was questionable with four. Three of these four specimens were studied at the beginning of the work, before the technic of concentration was perfected. In one instance there was no digitalis effect whatever. With the two fluids from questionably digitalized patients the results were doubtful. No response similar to the digitalis effect was obtained with any of the nine fluids from control patients who had not had any digitalis.

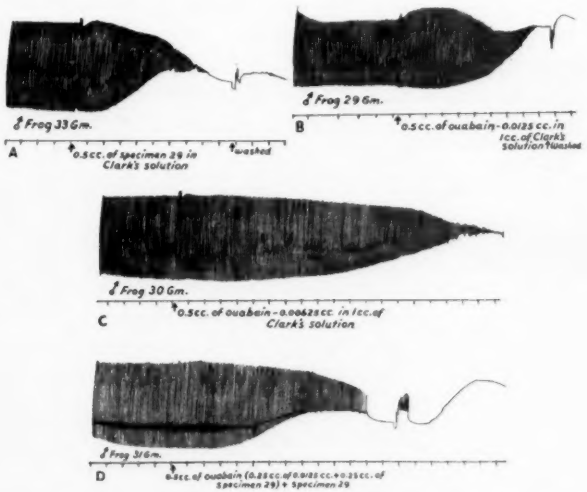
♂ Frog 33 Gm.
A
0.5 cc. of specimen 29 in Clark's solution
washed
♂ Frog 29 Gm.
B
0.5 cc. of ouabain-0.0125 cc. in 1 cc. of Clark's solution
♂ Frog 30 Gm.
C
0.5 cc. of ouabain-0.00625 cc. in 1 cc. of Clark's solution
♂ Frog 31 Gm.
D
0.5 cc. of ouabain (0.25 cc. of 0.025 cc. + 0.25 cc. of specimen 29) + specimen 29

Chart 4.—The combined ouabain method with a Straub preparation of the heart. *A*, the digitalis effect of 5,000 cc. of concentrated edema fluid from the leg. The heart stopped in eight minutes. *B*, the typical digitalis effect of a lethal dose of ouabain. Note that the heart stopped in nine minutes. *C*, a frog of approximately the same size was given half the dose of ouabain used to produce the curve in *B*. Note that the heart stopped in twenty minutes, taking approximately twice as long as in *B*. *D*, the curve of the combined effects of *A* and *C*. Half the dose used in *A* plus the same dose of ouabain used in *C* was used in the heart of a frog of approximately the same size. Systolic standstill was produced in twelve minutes. This amount of ouabain used alone should have taken about twenty minutes (as in *C*) to stop the heart.

The direct chemical tests for the presence of digitalis bodies on the whole have proved unsatisfactory. This is in accord with the experi-

ence of others.[25] The various fluids were tested by the Knudson-Dresbach quantitative method[26] and the Keller-Kiliani qualitative method.[27] With the former the results were negative; with the latter, five of eleven fluids gave positive results; all of which showed the presence of digitalis in the Straub preparation of the heart.

Finally, there is one more procedure to confirm the presence of active digitalis substances in the body fluids of digitalized patients. This consists in using the precipitate obtained by the chemical means, suspended in Clark's solution, combined with a sublethal dose of digitalis—the so-called combined ouabain method of Hatcher.[28] Into the ventral lymph sac of a live frog is injected a fraction of a known lethal dose of ouabain, the unknown substance is added and it is noted whether the combined action of the two substances gives a lethal digitalis

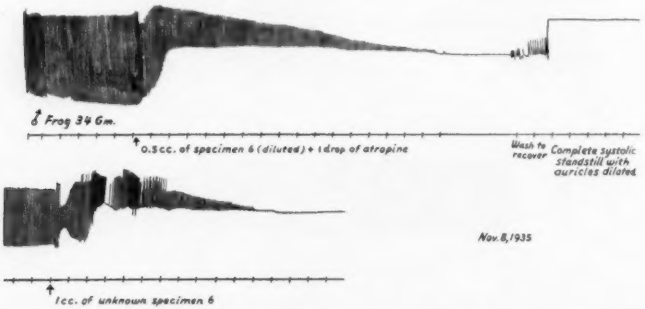
Frog 34 Gm.
0.5 cc. of specimen 6 (diluted) + 1 drop of atropine
Wash to recover
Complete systolic standstill with auricles dilated
Nov. 8, 1935
1 cc. of unknown specimen 6

Chart 5.—The digitalis effect of 1,250 cc. of ascitic fluid from a digitalized patient with an abdominal malignant growth. At first there was an unsatisfactory history of treatment with digitalis. The fluid showed a typical digitalis effect, uninfluenced by atropine—complete systole with mechanical irritation. Later information revealed that there had been regular treatment with digitalis before the patient's admission to the hospital. The lower curve represents the typical digitalis effect produced by the concentrated abdominal fluid. The upper curve shows the type of curve uninfluenced by the addition of atropine. After stoppage of the heart, mechanical irritation of the ventricle (accepted in digitalis assay methods) caused a complete systolic standstill with the auricles dilated.

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25. Lendle, L., and Schmelzer, W.: Ueber die Baljetsche Farbreaktion der Digitaliskörper, Arch. f. exper. Path. u. Pharmakol. **177**:622, 1935. Hanzlik, P. J., and Wood, D. A.: The Mechanism of Digitalis Emesis in Pigeons, J. Pharmacol. & Exper. Therap. **37**:67, 1929.

26. Knudson, A., and Dresbach, M.: A Chemical Method of Assaying the Active Principles of Digitalis, J. Pharmacol. & Exper. Therap. **20**:205, 1922.

27. Koch, F. C.: Practical Methods in Biochemistry, Baltimore, William Wood & Company, 1934, p. 63.

28. Hatcher, R. A.: The Persistence of Action of the Digitalins, Arch. Int. Med. **10**:268 (Sept.) 1912.

effect. This was done in two experiments. In the first experiment half the lethal dose of ouabain was given with the unknown substance, and death of the frog did not occur. In the second experiment three fourths of the lethal dose of ouabain plus the unknown substance produced a typical cardiac systolic standstill in sixty or sixty-five minutes. The same procedure was carried out also with the Straub preparation of the heart, three other concentrates of edema fluid being used. As shown in chart 4, adding the unknown substance to half the lethal dose of ouabain produced a typical summation effect in about the same time required by a lethal dose of ouabain alone. This gave further evidence that the material we were recovering from the body fluids of digitalized patients was a substance that acted synergistically with ouabain as well as like digitalis.

COMMENT

The curves showing a digitalis effect obtained with fluids removed from patients who had been taking the drug, the absence of such an effect with fluids from persons who had not taken digitalis and the synergistic action seen by the "combined ouabain method" of Hatcher have led us to believe that we have been able to recover active digitalis substance from the body fluids of digitalized patients. Whether the substance recovered in these instances is the cause of postdiuretic symptoms has not been solved by this study. Its presence in the body fluid, however, adds validity to our assumption, but further studies are necessary to substantiate or to discredit the idea of digitalis intoxication with diuresis. Other studies have suggested themselves, but sufficient data have not yet been obtained.

No attempt was made to estimate accurately the amount of digitalis contained in the various fluids analyzed in this study. A rough comparison between our curves and those obtained from known strengths of digitalis led us to the opinion that as much as the equivalent of 1 cc. or more of tincture of digitalis was present per liter of fluid. If this is true, it is conceivable that excretion of from 5 to 8 liters or more, which occasionally occurs within twenty-four hours after the administration of a mercury diuretic or a preparation like theophylline, may be adding as much as 0.5 Gm. or more of digitalis to an already digitalized heart. Added to cardiac muscle that is fully digitalized, such an amount of digitalis substance could easily provoke the symptoms of headache, giddiness, weakness, nausea and even vomiting.

SUMMARY AND CONCLUSIONS

A patient with cardiac disease who is digitalized and who yet shows peripheral edema or free fluid in the body cavities occasionally has symptoms of headache, nausea, vomiting, giddiness and lassitude after diuresis induced with salyrgan or mercurin or with theophylline. These

symptoms could be due to digitalis intoxication when the body fluids are excreted through the kidneys by way of the blood stream, if that body fluid contained digitalis substances.

On the basis of the chemical method of Schmidt, modified in terms of the physical properties of digitoxin, edema fluid from the pleurae, peritoneum and leg was treated and concentrated, with the recovery of a gray-white precipitate. This precipitate, suspended in Clark's solution, was placed in a Straub preparation of the frog heart to be tested for digitalis, and the results were recorded on a kymogram. These curves were compared with curves for known digitalis.

A total of twenty-nine specimens of fluid from twenty-four patients were examined. Eighteen fluids were from known digitalized patients. Thirteen of these gave positive evidence of digitalis by the biologic method. The results were questionable in four cases and negative in one case. Two specimens from patients with questionable digitalization gave doubtful results. Nine specimens of fluids from patients with tuberculosis, neoplasm or cirrhosis of the liver, none of whom had been given digitalis, were used as controls. None of these showed any digitalis effect.

Although no exact quantitative determinations were carried out for the thirteen fluids showing curves indicative of a digitalis effect, we believe the amount recovered was significant and sufficient to cause clinical symptoms in patients under the conditions discussed.

The Knudson-Dresbach reaction for the quantitative determination of digitalis glucosides was unsatisfactory in our experience. The qualitative Keller-Kiliani test for desoxycarbohydrate, though not specific and not highly sensitive, gave positive reactions for five of eleven specimens of fluid showing the digitalis effect by the biologic method.

It is believed that active digitalis substances are present in the body fluids of digitalized patients and that they can be recovered. Further studies are necessary, however, to confirm or to discredit the idea that these substances may give rise to symptoms of digitalis intoxication following diuresis.

NOTE.—Since this paper went to press a fully digitalized patient with poor compensation entered the hospital and after three successive administrations of salyrgan had prompt diuresis, headache and nausea (no vomiting) and twice became irrational. On two of these occasions during diuresis the electrocradiogram showed coupling during the symptoms not present before or after. During the second period of diuresis ammonium chloride was withheld, and there was a drop in the chloride content of the serum from 570 to 480 mg. per hundred cubic centimeters. On the other two occasions when the salt was given, no change in the chloride value occurred; yet the symptoms were the same during all three periods of diuresis.

EFFECT OF PARENTERALLY ADMINISTERED PEPTONE

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AND
LINDON SEED, M.D.
CHICAGO

The possibility of supplying the nitrogen requirements of the body parenterally led us to investigate the effect of protein split products given by this route. For many years reports have appeared in the literature on various phases of the phenomenon which has been designated "peptone shock." These have included elaborate chemical studies and physiologic observations made after the parenteral and oral administration of certain protein split products. This work has all been carried out with crude products of protein digestion. In consequence the results obtained have been variable and often contradictory.

REVIEW OF THE LITERATURE

In 1913 Henriques and Andersen [1] described experiments in which they maintained goats in positive nitrogen balance by means of intravenous injections. The authors achieved this by administering a solution containing completely digested (trypsin-erepsin) meat, dextrose, sodium acetate, sodium chloride, potassium chloride, calcium chloride and magnesium chloride by continuous intravenous drip. They concluded that protein synthesis can occur when these products are administered parenterally.

A year later the same authors [2] reported a similar experiment on a goat from which the intestinal tract had been removed, in order to prove that the gastro-intestinal tract took no part. The animal survived for three days, during which time it was shown to be in positive nitrogen balance. Further experiments with native proteins and also Witte's peptone were unsuccessful. Thompson [3] concluded that parenterally administered peptone and proteose are retained to the extent of 60 per

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1. Henriques, V., and Andersen, A. C.: Ztschr. f. physiol. Chem. **88**:357-369, 1913.

2. Henriques, V., and Andersen, A. C.: Ztschr. f. physiol. Chem. **92**:194-211, 1914.

3. Thompson, W. H.: J. Physiol. **25**:1-21 and 79-190, 1899-1900.

cent. He demonstrated a diuretic effect as the result of the injection, with a decrease in the output of nitrogen and urea per cubic centimeter but an increase in the output of total nitrogen and urea. He assumed that the proteoses were held in combination with globulin.

Buglia [4] concluded from experiments involving the intravenous injection of protein split products that amino-acids administered in this manner are burned or excreted through the kidney, their fate depending largely on the concentration of the solutions injected.

Biasiotti [5] studied the changes in the bile following the parenteral injection of Witte's peptone into dogs. He concluded that it was not injurious in amounts not in excess of 0.3 Gm. per kilogram if the kidneys were intact.

Fink,[6] in a study of the antigenic properties of proteoses, concluded that peptone shock is not anaphylactic and concurred with Underhill's [7] conclusions that their effect is due to proteoses.

Auld [8] also concluded that the activity of commercial peptones is dependent on their proteose content.

Gross [9] observed that the bloody diarrhea induced by a 0.3 Gm. per kilogram dose of Witte's peptone rapidly administered intravenously is prevented by atropine. He concurred with other authors in ascribing the effects of Witte's peptone to the proteose present.

More recently Urbach and Kitamura [10] arrived at much the same conclusion. On this ground they objected to the term peptone in connection with these products. They further showed that the effect of peptone on the uterine strip, as demonstrated by Jadassohn and Schaaf, is due to the potassium content of the solution of peptone.

Clark [11] concluded that the toxic effects were produced by the higher proteoses (the fraction precipitated by 80 per cent alcohol).

Mills [12] found that 48 cc. of a 10 per cent solution of peptone administered rapidly intravenously prevented the blood from clotting. When peptone was added to the blood in vitro the reverse effect was noted. The author ascribed this phenomenon to the neutralization of the thrombolytic substance in the blood, which in vivo is overcompensated

4. Buglia, G.: Arch. di fisiol. **24**:448-453, 1926.

5. Biasiotti, A.: Arch. di biol. **5**:43-54, 1928; Ber. f. d. ges. Physiol. **45**:783, 1928.

6. Fink, E. B.: J. Infect. Dis. **25**:97-123, 1919.

7. Underhill, F. P.: Am. J. Physiol. **9**:345-373, 1903.

8. Auld, A. G.: Brit. M. J. **1**:835-836, 1922.

9. Gross, E. G.: J. Pharmacol. & Exper. Therap. **30**:351-360, 1927.

10. Urbach, E., and Kitamura, S.: Klin. Wchnschr. **13**:1573-1575, 1934.

11. Clark, A. J.: J. Pharmacol. & Exper. Therap. **23**:45-54, 1924.

12. Mills, C. A.: Chinese J. Physiol. **1**:249-262, 1927; Am. J. Physiol. **76**: 642-650, 1926.

by the pouring out of this substance following its neutralization in the blood. He compared the process to a toxin-antitoxin reaction and said he considered it to be a true immune reaction.

Feldberg,[13] Wand [14] and others observed a drop in the blood pressure with accompanying symptoms of shock following the injection of peptone. Underhill,[15] on the other hand, injected a specially prepared protein split product and could demonstrate no change in blood pressure or coagulation.

Chahovitch [16] demonstrated hyperglycemia following the intraperitoneal injection of Witte's peptone. Nord [17] and Henderson and Underhill [18] also noted hyperglycemia following the parenteral administration of Witte's peptone.

Kaiwa [19] was unable to demonstrate any change in peptone hyperglycemia in dogs following bilateral splanchnicotomy and vagotomy and sympathectomy in the upper lumbar region. Nor was he able to demonstrate any increase in epinephrine as the cause. He concluded that the hyperglycemia is peripheral in origin.

Irving and Kay [20] found an increase in the dextrose in the corpuscles after the intravenous injection of peptone.

In contrast to these authors, Menten and Manning [21] found a marked variation in the effects of different samples of Witte's peptone on the sugar content of the blood, ranging from hyperglycemia to fatal hypoglycemia. McGuigan and Ross [22] observed hypoglycemia after the injection of small doses of peptone.

Schiff and his co-workers [23] concluded from their experiments that anoxemia was the cause of the hyperglycemia of shock induced by Witte's peptone. They found that epinephrine given during peptone shock caused further hyperglycemia as well as a rise in blood pressure. Insulin administered during peptone shock caused a sharp drop in the sugar content of the blood and a rise in blood pressure. These workers

13. Feldberg, W.: Arch. f. exper. Path. u. Pharmakol. **140**:156-167, 1928.

14. Wand, R. A.: Nature, London **117**:487, 1926.

15. Underhill, F. P.: Am. J. Physiol. **9**:345-373, 1903.

16. (*a*) Chahovitch, X.: Arch. internat. de physiol. **29**:298-300, 1927. (*b*) Chahovitch, X., and Arnovlevitch, V.: Compt. rend. Soc. de biol. **96**:16, 1927.

17. Nord, F.: Acta med. Scandinav. **65**:1-60, 1926; Compt. rend. Soc. de biol. **93**:1185-1188, 1925.

18. Henderson, Y., and Underhill, F. P.: Am. J. Physiol. **28**:275-277, 1911.

19. Kaiwa, T.: Tohoku J. Exper. Med. **20**:365-388 and 471-497, 1933.

20. Irving, J. T., and Kay, H. D.: J. Physiol. **61**:113-121, 1926.

21. Menten, M. L., and Manning, H. M.: J. Biol. Chem. **72**:255-260, 1927.

22. McGuigan, H., and Ross, E. L.: J. Biol. Chem. **22**:417-423, 1915; **30**:175-179, 1917.

23. Schiff, E.; Eliasberg, H., and Mazzeo, A.: Pediatria **38**:1158-1161, 1930; Jahrb. f. Kinderh. **128**:209-227, 1930; **129**:266-269, 1930; **134**:362-366, 1932.

reported also a marked lowering of the p_H and carbon dioxide content of the blood and an increase in the chloride, lactic acid, potassium and calcium contents.

Garofeanu and Lazar [24] found that associated with the shock induced by the injection of 0.15 Gm. of Witte's peptone per kilogram, the urea content of the blood was diminished in the majority of instances. Chahovitch [16a] demonstrated a drop in the cholesterol content of the blood during the first three hours after injecting from 2.5 to 22 cc. of a 5 to 20 per cent solution of peptone, followed by a rise which reached a maximum after from seventy-two to ninety-six hours.

EXPERIMENTS

It is apparent that these workers have confined their observations to the changes in peptone shock induced by the injection of crude mixtures consisting chiefly of proteose, usually in the form of Witte's peptone.[25] Henriques and Andersen used a somewhat more completely digested protein and may have succeeded in having it utilized, although the mere retention of nitrogen over the short period of observation reported is inconclusive.

Taking cognizance of these shortcomings in previous work on the subject, we used Difco bactopeptone, which, according to the analysis submitted by the manufacturers, is constant in composition and contains:

	Percentage
Total nitrogen	16.52
Coagulable nitrogen	None
Total proteose nitrogen	0.97
Primary proteose nitrogen (precipitable by saturation with zinc sulfate)	0.07
Secondary proteose nitrogen (precipitable by half saturation with zinc sulfate)	0.90
Peptone nitrogen	15.50
Free amino-acid nitrogen	1.69
Ammonia nitrogen	0.03
Amino nitrogen (determined by Van Slyke method)	2.32
Ash	2.87

Concentrations of 1, 5, 10, 20 and 30 per cent were used, and the solutions were carefully made up in sterile water and passed through a Berkefeld filter. A 1 per cent solution of Difco bactopeptone is hypotonic, causing hemolysis of the red blood cells; this concentration was made up in a buffered saline solution. Since solutions of peptone give a strongly positive reaction to the biuret test, the urine was collected and examined by this method.

24. Garofeanu, M., and Lazar, N.: Compt. rend. Soc. de biol. **95**:427-428, 1926.

25. Witte's peptone is a variable mixture of proteoses with relatively small amounts of peptone.

Our problem was to determine: first, the concentrations of solutions of proteose-free peptone tolerated when administered intravenously to an experimental animal; second, the effect of solutions of peptone on the excretion of urine; third, the effect of such intravenous injections on the blood and spinal fluid pressure; fourth, the effect of solutions of peptone on the chemical findings in the blood; fifth, the fate of the peptone injected, so far as that may be determined, and, sixth, whether or not Difco bactopeptone had any antigenic effect.

Two dogs were given a 20 or 30 per cent solution of peptone by the intravenous route daily in addition to a full diet. The details of this experiment are recorded in the accompanying table.

Experimental Data

	Date, 1934	Concentration of Solution of Peptone, %	Volume, Cc.	Time Taken for Injection, Minutes	Temperature		Weight, Pounds
					Before Injection, F.	After Injection, F.	
Dog 1	11/ 1	20	75	20	.....	.....	43
	11/ 3	20	300				
	11/ 4	20	300				
	11/ 5	20	300	..	.....	.....	43
	11/ 6	30	300	50	102.3	103.4	
	11/ 7	30	300	60	101.8	102.6	
	11/ 8	30	300	..	102.6	101.5	
	11/ 9	30	300	..	102.8	102.0	
	11/12	30	300	..	102.0	101.4	
	11/13	30	300				
	11/14	30	300				
	11/15	30	300	10	102.4	101.6	43
	11/16	30	300	..	102.9	102.0	
	11/17	30	300	15	101.7	101.2	
	11/19	30	300				
	11/20	30	300				
	11/21	30	300				
Dog 2	11/ 1	30	300				
	11/ 2	30	300				
	11/ 4	30	300				
	11/ 5	30	300				
	11/ 6	30	300	45	103.2	103.5	
	11/ 7	30	300				
	11/ 8	30	300	..	103.6	103.8	
	11/ 9	30	300	..	104.0	104.0	
	11/12	30	300				
	11/13	30	300				
	11/14	30	300				
	11/15	30	300	20	102.2	101.6	
	11/16	30	300	..	101.5	100.0	
	11/17	30	300	20	103.0	102.5	

It is apparent from the protocols that large quantities of peptone may be administered intravenously daily to dogs with no apparent deleterious effect. For the first nine days the temperature rose a maximum of up to 1 F. during injection of the peptone. After the ninth day the temperature fell as much as 0.9 F. during the injection. Petersen, Müller and Saelhoff [26] observed a similar reversal effect on the leukocytosis induced by peptone beginning on the eleventh day of the injections.

The third group of experiments was carried out to determine the effect of peptone on the blood and spinal fluid pressure.

26. Petersen, W. F.; Müller, E. F., and Saelhoff, C.: J. Immunol. **19**:165-175, 1930.

The blood pressure was determined by direct incannulation of the carotid artery, the fluctuations being recorded on a smoked drum. The spinal fluid pressure was obtained from a spinal needle inserted into the cisterna magna and attached to a water manometer. Direct readings were made at intervals and recorded. Peptone was injected at varying rates by means of a Woodyatt pump. Solutions of peptone of various concentrations were used.

The maximal changes in the blood pressure obtained with the concentrations of peptone used consisted of a drop in the systolic pressure of 10 mm. of mercury and a rise in the diastolic pressure of 5 mm. of mercury shortly after the beginning of the experiments (chart 10).

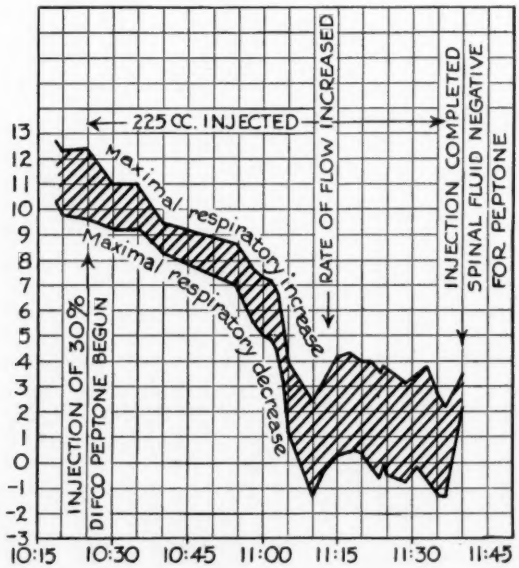

Chart 1.—The spinal fluid pressure in millimeters of mercury.

The spinal fluid pressure varied with the concentration of the solution of peptone. The injection of a 30 per cent solution of peptone (chart 1) resulted in a drop which was prompt and well sustained, reaching a negative value in many instances. Further, the spinal fluid in all instances gave a negative reaction to the biuret test.

Spinal fluid pressure is dependent on the osmotic balance between the blood and the tissues of the central nervous system, the freedom of circulation of the spinal fluid, the permeability of the capillaries and the venous pressure. The sharp reduction in spinal fluid pressure noted in these experiments is apparently dependent on the elevation of the osmotic pressure of the blood, with resulting dehydration of the central

nervous system. The absence of a secondary rise is due to the impermeability of the spinal fluid barriers to it.[27] The diuresis may be postulated as resulting from an increase in the osmotic pressure of the blood or from the tendency of the body to excrete the peptone as a foreign material, requiring a considerable volume of water as a vehicle of excretion, or from a combination of these two factors.

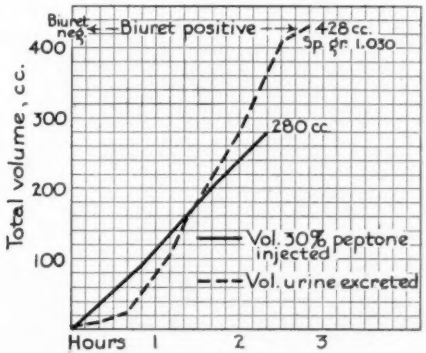

Chart 2.—The effect of an injection of a 30 per cent solution of peptone on the urinary output.

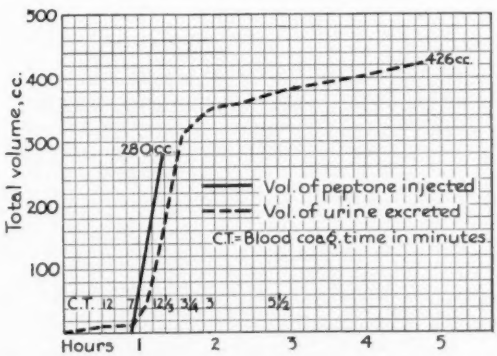

Chart 3.—The effect on the urinary output of a rapid injection of a 30 per cent solution of peptone.

In the second group of experiments the volume of urine excreted during the period of observation exceeded the volume of fluid injected when a 30 per cent solution of peptone was administered slowly (chart

27. Milles, G., and Hurwitz, P.: The Effect of Hypertonic Solutions on Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Tonicity, Arch. Surg. **24**:591-601 (April) 1932.

2). Indeed, the volume of urine excreted had already crossed the line of the injected volume after one hundred minutes, i. e., the output of urine exceeded the volume of injected fluid at any given moment after

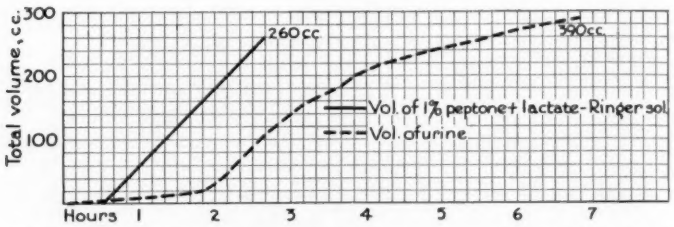

Chart 4.—The effect on the urinary output of a 1 per cent solution of peptone and buffer salts.

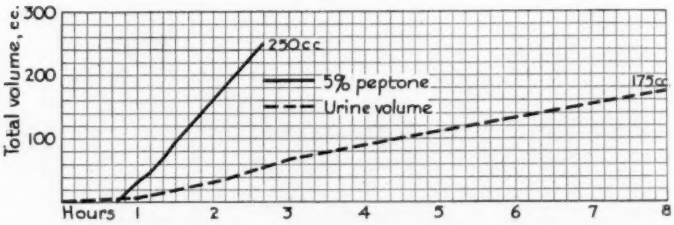

Chart 5.—The effect on the urinary output of a 5 per cent solution of peptone.

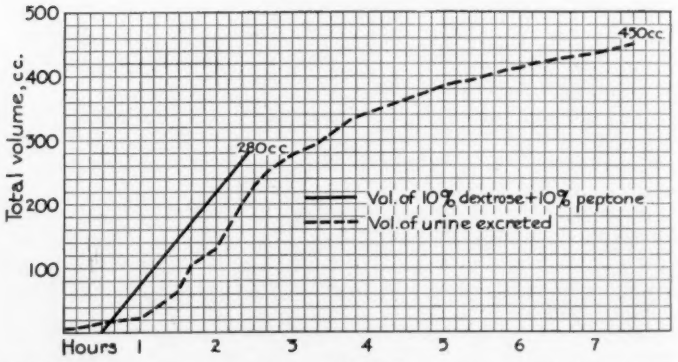

Chart 6.—The effect on the urinary output of a 10 per cent solution of peptone plus a 10 per cent solution of dextrose.

this time and continued to do so throughout the remainder of the experiment. When the rate of injection was rapid, the volume excreted paralleled the volume injected and did not exceed it until after the injection had been completed (chart 3).

When the injected solution contained less than 30 per cent peptone the diuretic effect was proportionately less (charts 4 to 6). However, with a 1 per cent solution of peptone in buffered saline solution, a 10 per cent solution of peptone and 10 per cent peptone in 10 per cent dextrose solution, the volume of urine excreted as shown by determinations made during the period of observation exceeded the volume of fluid injected plus the expected normal output of urine during this time. With a 5 per cent solution of peptone the volume of fluid injected was not equaled by the volume of urine during the period of observation.

The results of the chemical studies were charted for clarity (charts 7 to 10). It will be observed that the most constant features are a

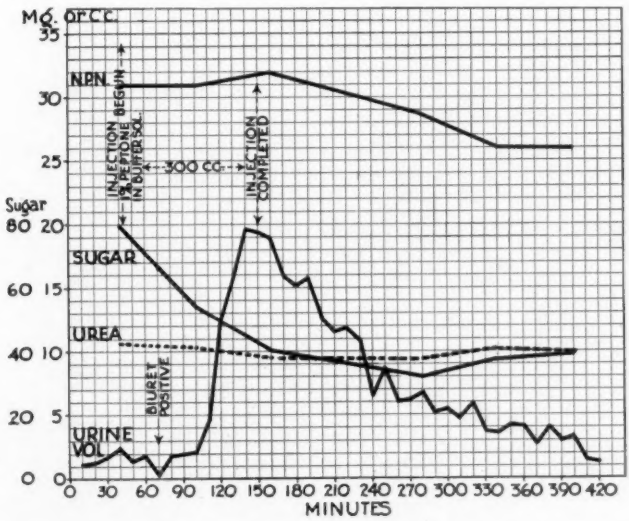

Chart 7.—Results of chemical studies.

primary elevation of the nonprotein nitrogen content and, to a less extent, the urea content, followed by a steady fall to a point below the original level when the experiments were closed. The sugar content of the blood tended to drop, except in the one experiment in which a 5 per cent solution of peptone was injected.

The results published here are not comparable with those of similar experiments reported in the literature, since we used a mixture of protein split products of constant composition, in no way comparable to Witte's peptone.

It was startling to find that as much as 500 cc. of 30 per cent Difco bactopeptone could be injected intravenously in many instances into a

dog with little reaction. The most marked untoward effects observed were an increased respiratory rate and vomiting. The slight rise in temperature which reversed on the ninth day to a fall, observed with daily injections of the solution, indicates a minor effect, which was possibly antigenic. The slight drop in blood pressure is indicative of a physiologic effect. When 300 cc. of a 15 per cent solution of Difco

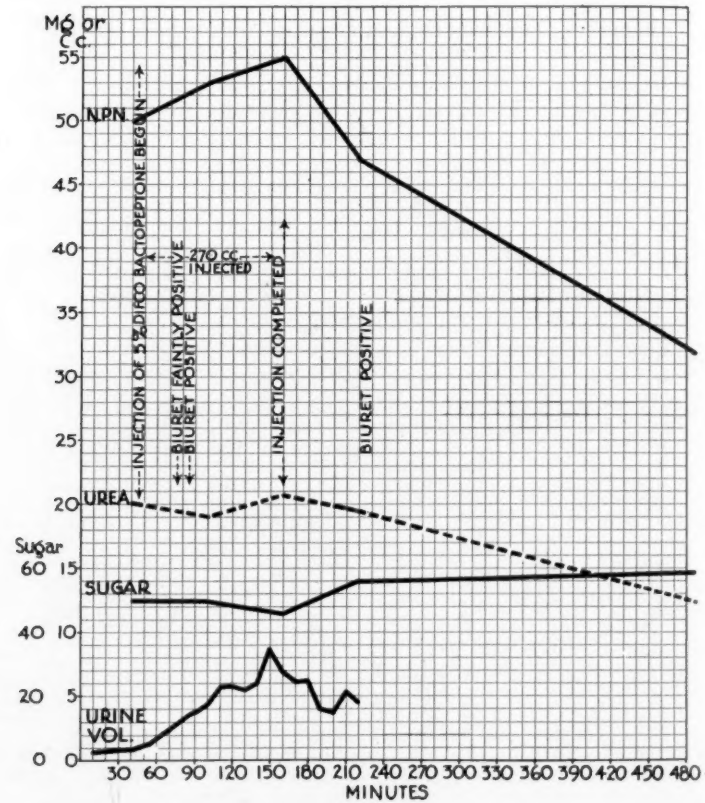

Chart 8.—Results of chemical studies.

bactopeptone was injected intravenously into a man, it failed to cause a reaction. However, a chill and fever resulted when a 20, 25 or 30 per cent solution was used.

The interval between the start of the injection and the appearance of peptone, if we may assume that the development of a positive reaction to the biuret test of the urine is adequate proof of the presence of peptone under the conditions of the experiment, varied up to ten

minutes, the longer period being observed when a 1 per cent solution of peptone was injected. It is well known that the presence of dextrose interferes with the development of the reaction to the biuret test. In the experiment in which peptone and dextrose were injected, the urine always failed to respond to the biuret test. However, shortly after the

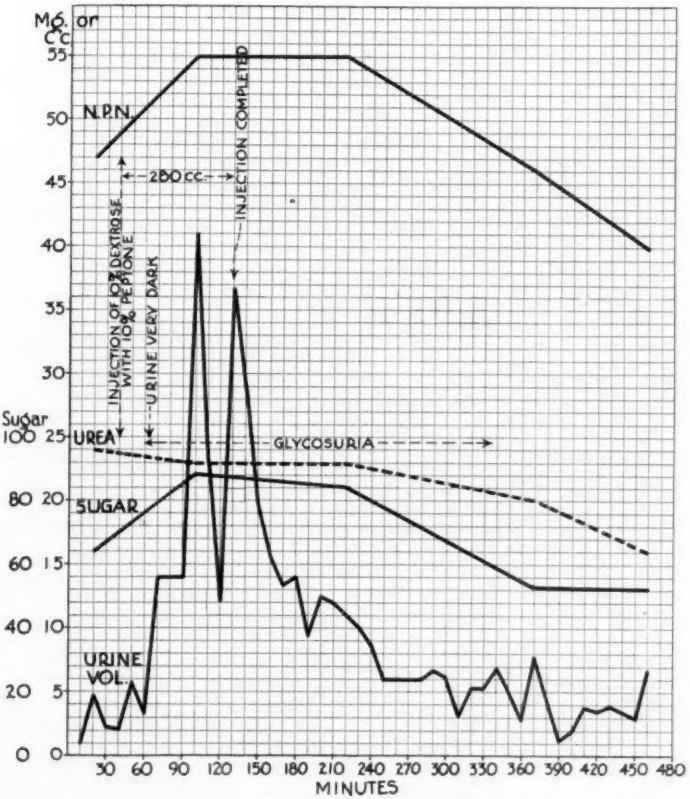

Chart 9.—Results of chemical studies.

start of the injection the urine became dark brown and was indistinguishable from the solution injected.

The changes noted in the blood chemistry parallel the urinary flow. They are characterized by a primary rise in the nonprotein nitrogen content, accountable for by the nitrogenous elements injected, and a secondary fall in the nonprotein nitrogen and the urea content, which is apparently merely the result of the washing out of these substances as part of the diuresis.

There are no criteria by which the utilization of parenterally injected protein split products can be determined. Henriques and Anderson assumed that the retention of nitrogen was sufficient. We cannot agree

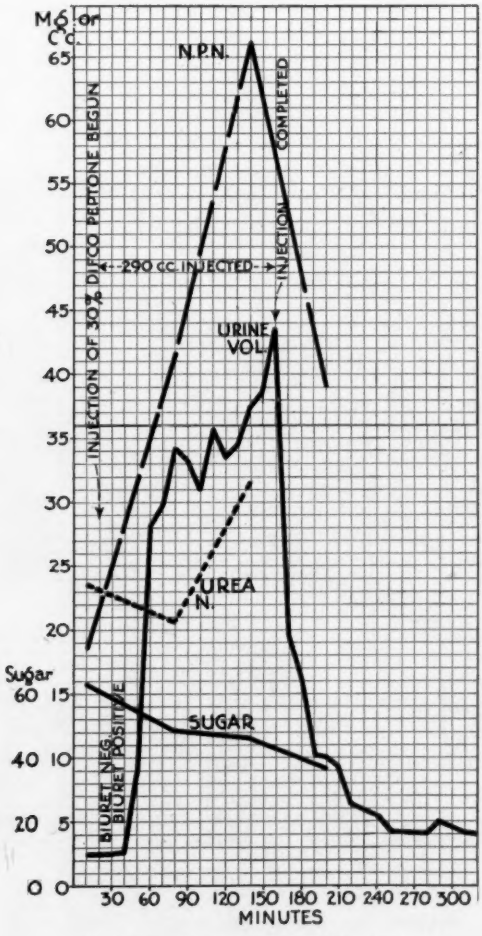

Chart 10.—Results of chemical studies.

with this assumption. It is possible that these products might be stored as such without utilization. Even a rise in the output of urea would in itself be inadequate evidence.

We have assumed that the rapid appearance in the urine of a substance giving a positive reaction to the biuret test indicates that the peptone is rapidly excreted. We have some evidence that this excretion is practically quantitative.

Miss Frances Briggs, of the department of physiological chemistry, was unable to adduce any evidence of precipitinogenic action in rabbits. In periods up to two weeks between injections in dogs, and in man, the evidence of antigenic effect noted was the change in the response of the temperture after the ninth day.

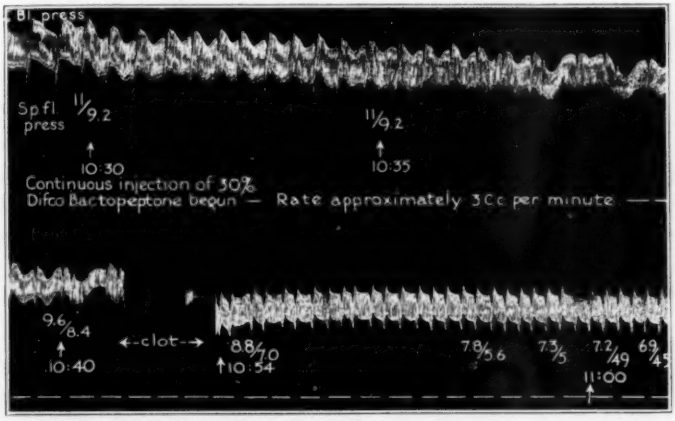

Chart 11.—Blood pressure tracings and spinal fluid pressure with regard to injection of Difco bactopeptone.

CONCLUSIONS

Difco bactopeptone was used as a low proteose-high peptone product of protein cleavage in a study of the effect of such a substance when injected parenterally.

Solutions of various concentrations of this peptone failed to cause perceptible damage when injected into dogs either in single doses or daily up to three weeks.

Diuresis of varying degree resulted, depending on the concentration of the solution and on the rate of injection.

A pronounced drop in spinal fluid pressure and a slight drop in blood pressure were noted.

Little change in the chemical findings in the blood resulted from the injection.

No antigenic effects were demonstrated.

DETERMINATION OF VITAMIN C SATURATION

A FIVE HOUR TEST AFTER AN INTRAVENOUS TEST DOSE

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ALFRED LILIENFELD, M.D.

AND

ELIZABETH MACLENATHEN, B.S.

NEW YORK

The response in terms of urinary excretion to a large dose of vitamin C administered orally has been widely used during the past few years as an indication of vitamin C saturation of the body.[1]

The amounts and the mediums (i. e., orange juice, tomato juice and crystalline vitamin C) have varied, but the method of administration has been by mouth. The possibility of error in such a test is now known to be great, owing to the variation in absorption and utilization of vitamin C from the gastro-intestinal tract as a result of varying degrees of acidity (anacidity), inflammation, the introduction of laxatives and other less understood factors. We have found this to be the case frequently.[2] The same objection holds for tests which involve studies of the blood level after the oral administration of this substance. Moreover, the level of excretion at which continued daily doses of 1 Gm. orally failed to cause any further increase and at which an intravenous dose demonstrated saturation varied widely for different persons. For example, in the case of three patients no further rise in urinary excretion could be obtained by the daily administration of 1 Gm. of cevitamic acid orally after twenty-four hour levels of 385, 503 and 207 mg. per hundred cubic centimeters, respectively, were reached. Four days after the oral doses were discontinued these patients

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The cevitamic acid used was furnished by Merck & Co., Inc., Rahway, N. J.

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital, Columbia University.

1. (*a*) Harris, L. J., and Ray, S. N.: Lancet **1**:71 (Jan. 12) 1935. (*b*) Johnson, S. W., and Zila, S. S.: Biochem. J. **28**:1393, 1934. (*c*) Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Lancet **2**:1399 (Dec. 21) 1935. (*d*) Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Am. J. M. Sc. **191**:319, 1936. (*e*) Wright, I. S.: ibid. **192**:719, 1936.

2. Wright.[1e] Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936.

excreted 900, 1,048 and 890 mg., respectively, in the first twenty-four hours after an intravenous dose of 1 Gm. of cevitamic acid. Such figures indicate definite saturation, as will be demonstrated later. This illustrates the difficulty in arriving at the percentage return level of an oral dose which by itself would accurately indicate the state of vitamin C saturation.

Studies of the cevitamic acid content of the blood and urine after intravenous doses were undertaken in an endeavor to obtain more reliable

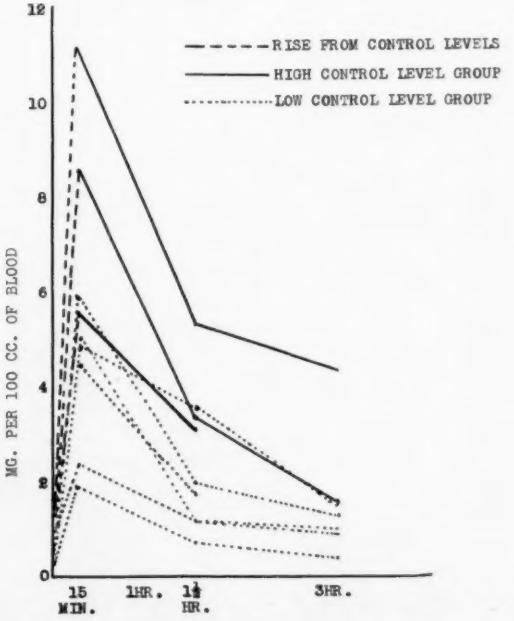

Chart 1.—Typical blood curves obtained after the intravenous injection of 1 Gm. of cevitamic acid.

information regarding vitamin C nutrition.[1e] It was found that after the intravenous injection of 1 Gm. of cevitamic acid in 10 cc. of physiologic solution of sodium chloride the cevitamic acid content of the blood reached a height which showed some relationship to the previous dietary intake and fell rapidly during the first hour and one-half, followed by a gradual return to a normal or slightly above normal level in three hours (chart 1). This drop was associated with a rise in urinary excretion, as illustrated in chart 2. In order to determine the length of

the interval between the injection of this substance and the beginning of its excretion by the kidneys, the following experiment was performed with the cooperation of Dr. Walter H. McNeill Jr.:

EXPERIMENT

Ureteral catheters were introduced by means of a cystoscope into the right and left ureters of normal adults. Control specimens of urine were collected. One gram of cevitamic acid dissolved in 10 cc. of physiologic solution of sodium

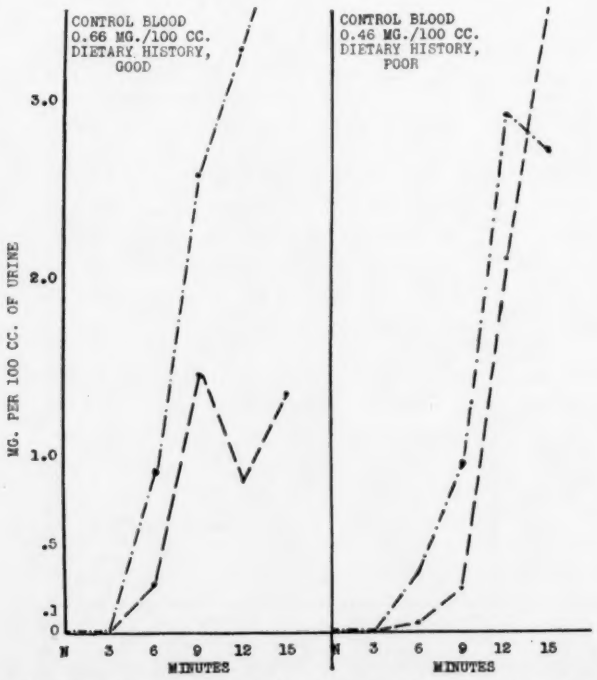

Chart 2.—The urinary excretion of cevitamic acid in two cases (patients G. S. and A. McG.). The dash line represents the excretion of the left kidney and the dot and dash line that of the right kidney.

chloride was injected intravenously. Thereafter specimens were collected from the separate ureters continuously for fifteen minutes. These were divided into three minute specimens, since the amount excreted in three minutes represented about the minimum volume needed for satisfactory study.

Two typical results may be seen in chart 2. The first three minute specimens failed to reveal any increase, the rise universally occurring between the third and the sixth minute. A low intake of vitamin C

with a low blood level did not affect either the length of the interval or the rapidity of rise during the first fifteen minutes both being within normal limits. This rise continued until a peak was reached between the first and the second hour, after which the rate of urinary excretion likewise began to decrease. This fall was rapid until the fifth hour, by which time the major portion of the total twenty-four hour return had been excreted. Persons in a normal state of vitamin C nutrition excreted at least 500 mg. of the 1 Gm. test dose in the following twenty-four hours. The actual amount depended on the degree of saturation. Of the amount excreted in the twenty-four hour period,

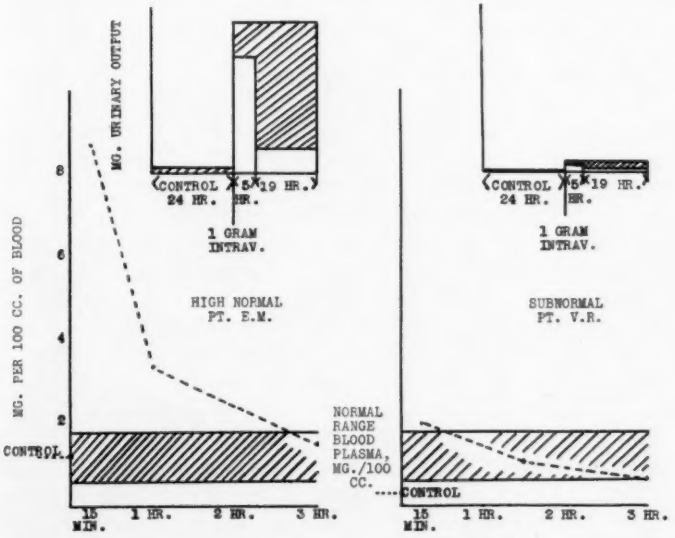

Chart 3.—Comparison of the blood curve and the urinary excretion of cevitamic acid after the injection of 1 Gm. of cevitamic acid for normal and subnormal persons. The total milligrams of urinary excretion indicated by the ordinates represents 1,000.

however, it was noted that 80 per cent or more was returned in the first five hours. In order to verify this observation a series of fifty-five tests were made using persons of varying degrees of vitamin C saturation.

TECHNIC

The subject was placed on a diet free from vitamin C for the twenty-four hours preceding the test and for the twenty-four hours after the administration of the test dose. During the control period the urine was collected and analyzed for excretion of vitamin C, standard precautions to prevent loss, which have been discussed in detail eleswhere,[10] being used. Briefly, the specimens were col-

lected in dark brown bottles, acidified to a p_H of 3 with sulfuric acid and kept at icebox temperature. Those excreted during the day were analyzed promptly. The night specimens were analyzed early each morning. The vitmin C content was determined throughout the experiment by a modification of Tillman's[3] 2,6-dichlorophenolindophenol method. At 9 o'clock on the morning of the test the patient voided, and immediately afterward 1 Gm. of cevitamic acid in 10 cc. of physiologic solution of sodium chloride was injected intravenously. The patient limited his fluid intake to the amount normally consumed at mealtimes, although the amount of urine excreted within the usual limits of fluctuation does not appear to affect the excretion of vitamin C. All urine passed during the first five hours after the injection was collected, including a specimen voided at exactly 2 p. m. This was immediately titrated for its vitamin C content. The remaining nineteen hour specimen was collected, with the precautions previously outlined, and titrated the next morning, immediately after the 9 a. m. specimen had been voided.

The results of six of the experiments were discarded as unsatisfactory. The results for the remaining forty-nine patients are presented in the accompanying table. A study of this table reveals certain interesting findings. In general, the patients with the best dietary history, control blood level and control twenty-four hour urinary excretion gave the highest responses to five hour and twenty-four hour tests. As the history and control findings were increasingly subnormal, the response to the test was proportionately less satisfactory. If such findings were consistent, the question might be raised as to the need for such a test. The data for patients 36, 37 and 38 may be mentioned as answering this question. As noted, the immediate dietary history was recorded as "fair to good" for the first two and "fair" for the last one. Inquiry revealed that each of these three patients, all with gastrointestinal disorders, had been on a limited diet for one week or less, long enough for the blood content and urinary excretion to drop to low levels; but the test dose demonstrated that marked tissue unsaturation had not as yet taken place. Thus, in our opinion, the first two figures may often be misleading regarding the actual state of vitamin C nutrition of the tissues, since they are subject to sudden fluctuations after temporary dietary changes. In only two other instances (patients 22 and 24) was the five hour excretion higher than was expected on the basis of the controlled studies. These readings were slightly over 400 mg. for the excretion in five hours (the low normal level). The nutrition of the tissues may have been better than we could determine by other methods. All except three patients excreted 80 per cent or more of their twenty-four hour output in the first five hours. These three excreted 75 per cent or more, and all fell within the normal group, excreting 400 mg. or more in five hours.

3. Tillman, J.; Hirsch, P., and Jackisch, J.: Ztschr. f. Untersuch. d. Lebensmitt. **63**:241, 1932.

It has been shown that fever per se produces a decrease in the excretion of vitamin C, probably because of increased metabolic demands. Persons with fever were found in all the nutritional groups in our series.

Data for Forty-Nine Patients

		Vitamin C				
			Urine			
Patient	Dietary History	Control Blood, Mg. per 100 Cc.	Control Specimen, Mg. per 100 Cc.	5 Hour Specimen, Mg. per 100 Cc.	24 Hour Specimen, Mg. per 100 Cc.	Excretion, Percentage*
1	Excellent	1.54	35.90	811.34	1,048.91	77.7
2	Good	1.40	36.00	809.65	900.50	89.9
3	Good	1.20	18.00	659.10	802.00	82.4
4	Good	1.10	10.00	536.49	634.68	84.5
5	Good	1.03	19.00	441.07	559.10	78.8
6	Good	1.01	.....	548.00	.....	....
7	Good	1.01	24.00	706.00	827.00	85.4
8	Good	0.93	.....	832.00	956.00	86.0
9	Good	0.90	18.00	407.60	485.80	83.8
10	Good	0.84	23.00	598.00	740.00	80.0
11	Fair	0.73	20.00	553.50	573.40	96.5
12	Fair	0.72	27.20	432.20	578.30	75.0
13	.....	0.71	.....	442.00	511.00	86.2
			Low Normal Level			
14	.....	0.68	.....	315.00	337.00	93.5
15	Fair	0.68	10.70	361.95	374.85	96.5
16	Poor	0.68	.....	.....	360.80	....
17	Poor	0.67	10.40	254.30	261.00	97.0
18	Poor	0.67	.....	221.00	241.00	91.7
19	Poor	0.65	.....	389.00	411.00	94.7
20	Fair	0.63	15.00	351.00	.....	....
21	Fair	0.61	17.00	346.00	375.00	92.1
22	Fair	0.57	14.50	413.50	467.90	92.3
23	Poor	0.59	.....	270.00	283.00	95.4
24	Fair	0.55	7.95	405.00	.....	....
25	Poor	0.54	13.50	207.40	244.31	84.9
26	Poor	0.52	14.00	297.00	307.00	96.6
27	Poor	0.52	.....	235.00	241.00	97.9
28	Fair	0.51	14.80	222.60	235.90	94.3
29	Poor	0.49	13.00	286.00	.....	....
30	Poor	0.47	19.00	297.00	311.00	95.2
31	Poor	0.46	11.00	227.00	238.00	95.3
32	Poor	0.45	12.50	135.10	144.30	93.6
33	Poor	0.44	13.60	99.12	116.67	83.2
34	Poor	0.43	.....	264.00	.....	....
35	Fair	0.42	.....	292.64	300.60	97.3
36	Fair to good	0.41	12.00	443.00	511.00	86.7
37	Fair to good	0.41	10.00	335.00	360.00	93.1
38	Fair	0.39	9.90	404.00	415.00	96.0
39	.....	0.39	.....	288.00	.....	....
40	Poor	0.39	18.50	189.10	197.87	93.0
41	Poor	0.39	....	95.00	.....	....
42	Poor	0.39	3.00	68.00	69.00	98.0
43	Poor	0.37	3.00	160.00	.....	....
44	Good	0.37	.....	76.00	89.00	84.6
45	Fair	0.35	11.00	168.00	185.00	91.1
46	Poor	0.34	18.80	143.57	162.70	88.0
47	Good	0.31	10.00	70.00	81.00	85.5
48	Poor	0.29	.....	118.00	.....	....
49	Poor	0.27	.....	68.00	.....	....

* The proportion of the twenty-four hour excretion obtained in the first five hours.

COMMENT

In eliminating the uncertainties of gastro-intestinal absorption and utilization, one major factor of error in determining vitamin C saturation in the body has been eliminated. The experiments outlined give definite knowledge of the subject's nutritional state with regard to

vitamin C in five hours, as compared with twenty-four hours. This has obvious advantages, such as its adaptability to ambulatory patients and as an aid when storage facilities, incontinence and poor cooperation are factors. Test doses of various sizes have been considered carefully, and 1 Gm. has been utilized for the following reasons: The size of this dose is such as to reduce the percentage of error in the actual titration when the figures are low. The figures are high enough so that slight variations in the dietary intake of vitamin C immediately preceding or during the test will produce only inconsequential effects on the results. The patient may even continue his normal diet without producing important changes in the results. The smaller the dose used, the greater the relative error introduced by the aforementioned factors. The problem of toxicity has also been considered. Thus far we have noted no evidence of toxicity or untoward effects following the injection of five hundred doses of 1 Gm. or more of cevitamic acid intravenously. One gram doses have been given daily for a month, and a number of doses of 5 Gm. each have been given with only one mild thermal reaction so far recorded. In that instance we were not sure that the cevitamic acid was responsible for the fever. There is therefore no known contraindication against 1 Gm. test doses thus far.

We therefore suggest the following technic for a five hour test for vitamin C saturation:

> Have the patient omit breakfast, void and discard the preliminary urine and receive the test dose of 1 Gm. of cevitamic acid in 10 cc. of physiologic solution of sodium chloride intravenously. Collect all the urine voided during the first five hours, including a specimen voided exactly at the end of the fifth hour. The technic of preservation and of titration have already been discussed. Titration should be done as soon after the five hour period as possible to avoid undue loss of the vitamin.

While such tests, using the urinary excretion after the intravenous injection of cevitamic acid, represent a distinct improvement over the oral test dose method, in that variations in absorption and utilization from the intestinal tract are eliminated, one is still confronted by the possibilities of variations in excretion due to impaired renal function and other factors of which there is little knowledge. For example, if the urinary output of vitamin C is low after the intravenous test dose, we have found in general that it indicates poor vitamin C saturation. It may mean in some rare instances that the excretory ability is poor. From the urine alone one cannot make a differentiation in such a case. If the blood curve [4] is studied at the same time, as indicated in

4. The studies of the blood in this work were carried out according to the method of Farmer and Abt (Farmer, C. J., and Abt, A.: Proc. Soc. Exper. Biol. & Med. **32**:1625, 1935).

chart 1, a differentiation may be made, since if the rate of excretion is retarded for any reason the elevation of the blood level will of necessity be prolonged, with a slower return to a normal level. More detailed studies of patients with varying types and degrees of renal damage must be made before this aspect of the problem will be understood.

It should be pointed out that tests of this type are not to be considered as indicating the presence or absence of scurvy. As previously noted,[1e] the state of unsaturation, as indicated by chemical studies of the blood and urine, may be present for a long time without the development of scurvy. On the other hand, saturation may be chemically achieved while the manifestations of scurvy are still present, although this state will not continue long. We believe that increased capillary fragility still remains the earliest definite evidence of scurvy. It should not, however, be regarded as pathognomonic of that disease.

SUMMARY

A five hour test, made after the intravenous injection of 1 Gm. of cevitamic acid, to determine the degree of vitamin C saturation in the body is proposed.

Studies are reported which demonstrate that 500 mg. or more of the 1 Gm. dose is normally excreted in the first twenty-four hours and that 400 mg. or more (80 per cent) of that is excreted in the first five hours.

This test gives, in our experience, a more reliable estimation of the actual state of vitamin C saturation in the body than any other method hitherto available. Studies of the blood, as outlined, may be made coincidentally for additional information.

In addition, this method presents the obvious advantages of a five hour test suitable for ambulatory patients and for daily hospital use as a routine.

FUNICULAR DEGENERATION OF THE SPINAL CORD WITHOUT PERNICIOUS ANEMIA

NEUROLOGIC ASPECTS OF SPRUE, NONTROPICAL SPRUE AND IDIOPATHIC STEATORRHEA

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Subacute combined degeneration of the spinal cord has come to involve a major problem that centers about the type of degeneration seen typically in pernicious anemia. More than sixty associated conditions or causes have been advanced for combined degeneration that often is said to be "just like that of pernicious anemia" (table 1). In some instances involvement of posterior and lateral columns, regardless of the absence of the usual status spongiosus or the presence of prominent fibrillar gliosis, fills the requirement of "like"; in others an occasional focus of perivascular demyelinization, regardless of its nature or topography, or degeneration of the posterior roots with secondary degeneration in the posterior column suffices; too much confidence may be placed in a typical or suggestive clinical picture of combined degeneration, or an unusual clinical picture may pass without comment. Criteria needed to rule out pernicious anemia or some kindred disturbance often are left unmentioned.

The typical picture in an unusual setting is almost unique and always suggests pernicious anemia in disguise. The legitimate and important question has been raised before as to the accuracy and implications of some of these observations and as to whether the typical clinical and pathologic picture does not carry with it an import that in some manner attaches specifically to a factor unknown but commonly associated with pernicious anemia. Bremer [1] has aptly said that the greatest industry on the part of a reviewer will not permit a critical review of the subject. Numerous investigators have attempted to penetrate the problem accen-

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Read at the meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1936.

1. Bremer, F. W.: III. Zentralnervensystem und perniziöse Anämie, Ergebn. d. inn. Med. u. Kinderh. **41**:143-201, 1931.

tuated by the remarkable discovery of the unique therapeutic value of liver by Minot and Murphy in 1926.[2]

The subject may be presented more pointedly by hazarding a few comments concerning the conditions with which subacute combined degeneration of the spinal cord has been associated or to which it has been attributed. These have been listed, for the sake of convenience, under several headings.

TABLE 1.—*Conditions Associated with or Frequently Considered to Be the Cause of Subacute Combined Degeneration of the Spinal Cord "Like That Seen in Pernicious Anemia"*

Endocrine Dysfunction	Infectious Diseases	Nutritional Disorders*	Poisoning	Miscellaneous Diseases
Acromegaly	Respiratory diseases	Alcoholism	Absinth	Anemia, splenic
Addison's disease	Chorea	Beriberi	Arsenic	Anemia, secondary
Diabetes mellitus	Diphtheria	Dysentery	Barium	Amyotrophic lateral sclerosis
Exophthalmic goiter	Erysipelas	Gastric carcinoma	Chloral	Ancylostomiasis
Myxedema	Influenza	Obstruction of bowel	Ergot	Arteriosclerosis
	Malaria	Carcinoma of pancreas	Lathyrus	Infestation with Bothriocephalus
	Measles	Pancreatitis	Lead	Caisson disease
	Leprosy	Pernicious anemia	Morphine	Icterus, hemolytic
	Rabies	"Prepernicious" anemia	Phosphorus	Jaundice
	Scarlet fever	Pellagra	Phosphin	Leukemia
	Sepsis	Scurvy	Strychnine	Nephritis
	Smallpox	Sprue	Tea	Pregnancy
	Syphilis			Primary degeneration
	Tetanus			Senility
	Typhoid			Shock
	Typhus			Unclassified disease
	Tuberculosis			

* Or those in which there may be an associated nutritional factor.

ENDOCRINE DISORDERS

In a patient with Addison's disease with signs of subacute combined degeneration of the spinal cord Hurst and Bell [3] found hematologic changes of pernicious anemia, and they said they regarded the anemia as underlying the neurologic picture in these cases. Maestrini [4] did not put it so clearly in reporting a case of acromegaly associated with pernicious anemia and combined degeneration but stressed a pluriglandular relationship.

Changes in the spinal cord that are associated with diabetes, although long under scrutiny, are still imperfectly understood. Changes in the

2. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470-476 (Aug. 14) 1926.

3. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anaemia, Achlorhydria and Intestinal Infection, Brain **45**:266-281 (Oct.) 1922.

4. Maestrini, D.: Sindrome neuro-anemica in acromegalica, Fisiol. e med. **3**: 695-708, 1932.

posterior columns,[5] changes in the posterior and lateral columns[6] and changes in the posterior, lateral and anterior columns of the spinal cord[7] have been observed in cases of diabetes. Williamson[5h] and Schweiger[5e] found degeneration in the intramedullary portion of the posterior roots of the spinal nerves in cases of diabetes and regarded the changes in the posterior columns as secondary. Czoniczer[8] reported a case in which diabetes was complicated by funicular myelitis. The neurologic changes in this case were similar to those which occur in cases of pernicious anemia. Vibratory sensibility was not mentioned, and there was no report of a gastric analysis. The changes which were illustrated suggested those seen in the spinal cord in cases of pernicious anemia, but the clinical symptoms seemed to outweigh the pathologic features noted in the spinal cord. The gray as well as the white matter was involved. The results of examination of the peripheral nerves were not reported. In the case of diabetes reported by Schwab and Schwab[9] combined degeneration of the spinal cord, Parkinson's syn-

5. (*a*) Bramwell, Byrom: Diabetes; Perforating Ulcer of the Foot; Advanced Atheroma of the Posterior Tibial Artery, the Artery Being Adherent to the Posterior Tibial Nerve; Marked Changes in the Posterior Tibial and Plantar Nerves, Clin. Studies **5**:279-290, 1907. (*b*) Hensay, Joseph: Untersuchungen des Central-Nervensystems bei Diabetes mellitus, Strassburg, C. & J. Goeller 1897. (*c*) Kalmus, Ernst: Beitrag zur Kenntnis der Rückenmarkserkrankungen bei Diabetes mellitus, Ztschr. f. klin. Med. **30**:559-572, 1896. (*d*) Sandmeyer, Wilhelm: Beitrag zur pathologischen Anatomie des Diabetes mellitus, Deutsches Arch. f. klin. Med. **50**:381-392, 1892. (*e*) Schweiger, L.: Ueber die tabiformen Veränderungen der Hinterstränge beim Diabetes, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **14**:391-405, 1908. (*f*) Souques, A., and Marinesco, G.: Lésions de la moelle épinière dans un cas de diabète sucré, Rev. neurol. **5**:242-245, 1897. (*g*) Williamson, R. T.: Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus, Brit. M. J. **1**:398-399 (Feb. 24) 1894; (*h*) Changes in the Spinal Cord in Diabetes Mellitus, ibid. **1**:122-123 (Jan. 16) 1904; The Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus, Rev. Neurol. & Psychiat. **5**:550-556, 1907; Diseases of the Spinal Cord, London, Frowde, Hodder and Stoughton, 1908, p. 371, footnote 3, reference 2.

6. Leyden: Bemerkungen über Diabetes mellitus, Deutsches Med.-Ztg. **14**:497-500 and 507-511, 1893.

7. Leichtentritt, Heinrich: Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893. Nonne, M.: Ueber Poliomyelitis anterior chronica als Ursache einer chronisch-progressiven atrophischen Lähmung bei Diabetes mellitus, Berl. klin. Wchnschr. **33**:207-212 (March 9) 1896. Ossokine, N.: Contribution à l'étude de l'anatomie pathologique de la moelle dans le diabète sucré, abstr., Rev. neurol. **10**:993, 1902.

8. Czoniczer, Gabriel: Ein mit Myelitis funicularis komplizierter Fall von Diabetes, Deutsche Ztschr. f. Nervenh. **104**:286-296 (Aug.) 1928.

9. Schwab, S. I., and Schwab, R. S.: Pernicious Anemia and Combined System Disease with Diabetes Mellitus and Parkinsonian Syndrome, Arch. Neurol. & Psychiat. **35**:126-130 (Jan.) 1936.

drome and pernicious anemia also were present. Some of the most severe disabilities of a neurologic order that we have observed in cases of diabetes included great weakness in the proximal muscles of the limbs, incontinence of urine and an increase in the amount of protein in the spinal fluid. The pathogenesis of these findings is unknown to us. Degeneration of the peripheral nerves, presumably on an arteriosclerotic basis, appears to be the most common neurologic feature associated with diabetes.[10]

Schilling's [11] patient with funicular myelitis and exophthalmic goiter recovered after thyroidectomy. Vibratory sensibility and the results of gastric analysis and hematologic examination were not mentioned. We have observed several patients who showed myxedema associated with observations that suggested involvement of the posterior and lateral funiculi; the patients improved as a result of treatment with thyroid preparations. There is no report of a necropsy in any of these cases.

INFECTIOUS DISEASES

Munch-Petersen [12] reported a case of a condition for which he preferred the designation encephalomyelitis funicularis infectiosa and in which the clinical symptoms and signs resembled those found in pernicious anemia. The hematologic picture was not that of pernicious anemia. The results of gastric analysis were not included. Necropsy disclosed marked degeneration of the posterior columns, including the portion adjacent to the posterior horns, which may have resulted from degeneration of the posterior roots of the spinal nerves. Degeneration of the pyramidal and cerebellar tracts, perivascular lymphocytic infiltration of both white and gray matter and degeneration of the anterior horn cells were also noted. Many different viruses may produce this picture. Perivascular demyelinization is not uncommon in a number of the virus diseases. Munch-Petersen expressed the opinion, as did Bremer, that paresthesias of the hands and feet, which were present, are characteristic of involvement of the posterior column of the spinal cord. However this may be, paresthesias with degeneration of the peripheral nerves and without degeneration in the spinal cord have been observed in cases of pernicious anemia by Hamilton and Nixon.[13]

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10. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576-603 (Oct.) 1929.

11. Schilling, Erich: Ein Fall von Myelitis funicularis bei Basedowscher Krankheit, Deutsche Ztschr. f. Nervenh. **91**:296-299 (May) 1926.

12. Munch-Petersen, C. J.: Encephalomyelitis disseminata (Redlich) und Encephalomyelitis funicularis infectiosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:451-492, 1934.

13. Hamilton, A. S., and Nixon, C. E.: Sensory Changes in the Subacute Combined Degeneration of Pernicious Anemia, Arch. Neurol. & Psychiat. **6**:1-31 (July) 1921.

Perivascular demyelinization, nests of glia cells, "fleabite" hemorrhages and thrombosis of small vessels are not uncommonly observed in infectious diseases of various kinds and may occur in the spinal cord as well as in the brain.

For many of the diseases listed, no reference is given. One of Dürck's [14] articles is often referred to as proving that combined degeneration of the spinal cord, like that which is seen in cases of pernicious anemia, may be caused by malaria. In the first of these articles Dürck described purpuric hemorrhages and *Ringwallherdchen* as occurring in certain parts of the central nervous system in a number of diseases, and in speaking of typhus he included involvement of the spinal cord. In the second article, which dealt with malaria specifically, he did not mention the spinal cord at all. Malarial encephalitis, he observed, may present the clinical picture of multiple sclerosis.

Scherer [15] described an unusual illness of 5 monkeys. The pathologic picture resembled that of the combined degeneration of the spinal cord that is associated with pernicious anemia. The striking feature was the epidemic onset with diarrhea. Since the disease did not affect man and the exact nature of the condition remained in doubt, this excellent report is only mentioned in passing.

NUTRITIONAL DISTURBANCES

The conditions placed tentatively under nutritional disturbances bid fair to throw light on the problem, which seems to have been brought much nearer solution by the studies of the gastric juice by Castle, Heath and Strauss; [16] Greenspon,[17] and others and by the response of subacute combined degeneration of the type seen in pernicious anemia to liver therapy.

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14. Dürck, Hermann: Die pathologische Anatomie der Malaria, München. med. Wchnschr. **68**:33-37 (Jan. 14) 1921; Veränderungen im Zentralnervensystem bei Infektions-, Intoxikations- und Blutkrankheiten, Wien. klin. Wchnschr. **40**: 181-182 (Feb. 10) 1927.

15. Scherer, H. J.: Funikuläre Spinalerkrankung mit schwerer Beteiligung des Grosshirnmarkes und Opticusveränderungen bei fünf Pavianen, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:212-234, 1932.

16. Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having no Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am. J. M. Sc. **182**:741-764 (Dec.) 1931.

17. Greenspon, E. A.: The Nature of the Antipernicious Anemia Principle in Stomach: I. Method to Improve Stomach Preparations, J. A. M. A. **106**:266-271 (Jan. 25) 1936.

The results of the investigations of Salus and Reimann,[18] if verified, possibly may lead to the discovery of a physiologic principle of the greatest importance. These investigators determined that Castle's intrinsic factor was present in 5 cases in which the usual clinical picture of subacute combined degeneration of the spinal cord, achylia and a normal hematologic picture were observed. They determined the presence of this factor by reenforcing liver therapy with gastric juice obtained from these patients and feeding it to patients known to have pernicious anemia. They further determined that Castle's intrinsic factor was not present in 7 cases in which subacute combined degeneration, achylia and the hematologic picture of pernicious anemia were observed. They concluded that the presence of Castle's intrinsic factor bears no obligatory relationship to subacute combined degeneration of the spinal cord but is related only to the hematologic picture. They proposed the term hemogen for the hematopoietic factor and the term neurogen for the neurotrophic factor.

For years there has been a question as to whether the neurologic complications of chronic alcoholism are primarily attributable to alcohol or occur through some intermediate process. Hurst [19] expressed the view that in 3 of his patients with pernicious anemia the achlorhydria may have resulted from chronic alcoholism, and strong arguments for assuming a dietary deficiency as a factor in the production of alcoholic polyneuritis were advanced by Minot, Strauss and Cobb.[20] Strauss [21] allowed 10 patients who were suffering from alcoholic polyneuritis to continue their customary daily intake of spirituous liquor on condition that they consumed a well balanced diet with a high vitamin content and supplemented with yeast or its products. They were also given concentrates of vitamin B and liver extract by parenteral injection. Improvement in the polyneuritis occurred in every instance. Nonne's [22]

18. Salus, Fritz, and Reimann, F.: Das Castlesche Ferment und die funikuläre Spinalerkrankung: Ein Beitrag zur Pathogenese des nervösen Krankheitssyndroms (VI. Untersuchungen zur Leberwirkung bei der Anaemia perniciosa), Klin. Wchnschr. **13**:986-990 (July 7) 1934.

19. Hurst, A. F.: La dégénérescence combinée subaiguë de la moelle et ses rapports avec l'anémie pernicieuse: L'anachlorhydrie et les intoxications intestinales, Ann. de méd. **24**:5-23 (June) 1928.

20. Minot, G. R.; Strauss, M. B., and Cobb, Stanley: "Alcoholic" Polyneuritis: Dietary Deficiency as a Factor in Its Production, New England J. Med. **208**:1244-1249 (June 15) 1933.

21. Strauss, M. B.: The Etiology of "Alcoholic" Polyneuritis, Am. J. M. Sc. **189**:378-382 (March) 1935.

22. Nonne, M.: Ueber Myelitis intrafunicularis und über kombinierte Strangerkrankung bei Alcoholismus chronicus: Kasuistik zur hämorrhagischen Diathese beim chronischen Alkoholismus, Monatschr. f. Psychiat. u. Neurol. **20**:497-528, 1906.

article on subacute combined degeneration of the spinal cord in cases of chronic alcoholism is a classic. Most of his cases were on the whole so carefully described and, incidentally, his illustrations and his instructive remarks were so convincing that there is no doubt that his 6 cases fill the requirements of the familiar picture of subacute combined degeneration of the type seen in pernicious anemia. One is left somewhat in the dark, however, as to just what was meant by his recurring notation that the stomach was normal as to motor and chemical functions. The macrocytosis or hyperchromic anemia in cases 2, 4, 5 and 6 and the hyperplastic bone marrow in cases 4, 5 and 6 certainly suggested pernicious anemia; in 1 case the author himself made this diagnosis. There are three possibilities: First, the alcohol itself may have been responsible; second, some cases of pernicious anemia inadvertently may have been included in the thousands of cases of severe chronic alcoholism, and third, some deficiency factor induced by alcoholism may have come into play. In Fleischmann's [23] series of alcoholic addicts, to which reference is often made, signs of involvement of the pyramidal tracts were prominent, but rapid recovery often occurred when the use of alcohol was discontinued. No necropsies were reported in these cases. In Ossenkopp's [24] case of chronic alcoholism, which also is frequently referred to, the symptoms suggested multiple sclerosis, but the pathologic picture could hardly be said to resemble that usually seen in pernicious anemia, and the author himself called it atypical.

The principal neuropathologic change in cases of berberi is neuritis.[25] In cases 7 and 8 in the report of Dürck [25a] the posterior columns of the spinal cord were severely involved, but the involvement was perhaps suggestive of secondary degeneration. In case 7 there was a suggestion of occasional ballooning of the nerve fibers, and the cerebellar tracts were incompletely involved.

Funicular myelitis has been described as following bacillary dysentery,[26] but in the cases reported the clinical picture was atypical, and necropsy was not performed.

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23. Fleischmann, Rudolf: Zur Lehre von der Myelitis funicularis: Ueber heilbare und abortive Formen von Myelitis funicularis, Deutsche Ztschr. f Nervenh. **51**:402-437, 1914.

24. Ossenkopp, G.: Atypische funikuläre Myelose mit Psychose bei chronischem Alkoholismus, Deutsche Ztschr. f. Nervenh. **117-119**:350-370, 1931.

25. (*a*) Dürck, Hermann: Untersuchungen über die pathologische Anatomie der Beri-beri; ein Beitrag zur normalen und pathologischen Anatomie des peripherischen Nervensystems, Beitr. z. path. Anat. u. z. allg. Path., supp. 8, 1908, pp. 1-176. (*b*) Wright, Hamilton: Changes in the Neuronal Centres in Beri-Beric Neuritis, Brit. M. J. **1**:1610-1616 (June 29) 1901.

26. Menzel, Werner: Ueber zwei Fälle von Polyneuritis und funikulärer Myelose nach bazillären Ruhr, Deutsche Ztschr. f. Nervenh. **126**:265-284, 1932.

The clinical and pathologic evidence that gastric carcinoma may have some etiologic relationship to typical subacute combined degeneration is too strong to be disregarded.[27] That subacute combined degeneration of the spinal cord may occur with benign tumors of the stomach also has been suggested.[28] Metastatic involvement of the roots of the spinal nerves or the spinal cord may lead to a confusing picture.[29] The case for carcinoma of the small intestine is not so strong.[28] The hematologic picture of pernicious anemia has been observed with carcinoma of the colon,[30] and in cases of carcinoma the hematologic picture of pernicious anemia has been associated with the clinical signs of subacute combined degeneration of the spinal cord.[31] The hematologic picture of pernicious anemia has been noted also in association with stricture of the small bowel,[30] and in some cases in which this association occurred there also were paresthesias.[32] In a case reported by Salus [33] stenosis of the small bowel, acquired achlorhydria, a normal hematologic

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27. Fisher, J. A.: Zur Frage der Myelosen nach Tuberkulose und Carcinom, Deutsche Ztschr. f. Nervenh. **134**:300-305, 1934. Garvey, J. L., and Stern, L. D.: Combined Sclerosis of the Spinal Cord and Carcinoma of the Stomach: Report of a Case, Am. J. M. Sc. **168**:847-852 (Dec.) 1924. Lubarsch, O.: Ueber Rückenmarksveränderungen bei Carcinomatösen, Ztschr. f. klin. Med. **31**:389-415, 1897. Simpson, C. K.: A Case of Addison's Anaemia with Subacute Combined Degeneration of the Cord Associated with Carcinoma of the Stomach, Guy's Hosp. Rep. **81**:392-406, 1931. Waterfield, R. L.; Shackle, J. W., and Hurst, A. F.: The Diagnosis of Addison's (Pernicious) Anaemia: Two Cases of Severe Anaemia, ibid. **73**:206-224, 1923.

28. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Stomach, Ann. Surg. **85**:354-359 (March) 1927.

29. Weber, F. P., and Hill, T. R.: Complete Degeneration of the Posterior Columns of the Spinal Cord with Chronic Polyneuritis in a Case of Widespread Carcinomatous Disease Elsewhere, J. Neurol. & Psychopath. **14**:57-60 (July) 1933. Weil, Arthur, and Kraus, W. M.: Cancer of the Spinal Cord, Am. J. M. Sc. **171**:825-836 (June) 1926.

30. Becker, Gösta: Liver Treatment in Diseases with a Blood Picture of Pernicious Anemia, Acta med. Scandinav., supp. 34, 1930, pp. 70-74.

31. Grinker, R. R.: Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, Arch. Int. Med. **38**:292-302 (Sept.) 1926. Little, W. D.; Zerfas, L. G., and Trusler, H. M.: Chronic Obstruction of the Small Bowel: The Result of Two Entero-Enterostomies and Apparently the Cause of Pernicious Anemia, J. A. M. A. **93**:1290-1291 (Oct. 26) 1929. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture (with One Liver-Treated Case), Acta med. Scandinav. **72**:231-240, 1929.

32. Hurst, A. F.: A Case of Addison's Anaemia with Subacute Combined Degeneration of the Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of the Ileum, Guy's Hosp. Rep. **83**:47-52 (Jan.) 1933.

33. Salus, Fritz: Zur Entstehung der funikulären Myelitis, Klin. Wchnschr. **11**:237-240 (Feb. 6) 1932.

picture and signs of subacute combined degeneration of the spinal cord were noted, but the spinal cord was not examined at necropsy. We observed a woman aged 60 who had multiple intestinal fistulas and a fecal fistula following appendectomy; later, the hematologic and neurologic picture of pernicious anemia developed, and typical subacute combined degeneration was verified at necropsy.

Baló [34] described a case in which funicular myelitis was associated with obstruction at the papilla of Vater, degeneration in the tail of the pancreas, marked increase in the islands of Langerhans and some lymphocytic infiltration. The illustrations which were included might pass for those of advanced degeneration of the spinal cord in a case of pernicious anemia. Inconstant paresthesias, ataxic paraplegia, absence of the patellar and achilles tendon reflexes, the presence of the Babinski reflexes and loss of cutaneous sensibility below the distribution of the fourth lumbar segment were noted. Baló said there had been no signs of pernicious anemia, but he did not say how the presence of this condition had been excluded. In 1 of our cases, that of a man aged 36 who had been subjected to cholecystectomy elsewhere and had then vomited uncontrollably, a psychosis, objective evidence of peripheral multiple neuritis and flaccid paralysis of the sphincters developed. The value for the hemoglobin was 65 per cent, and there were 3,820,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded. The patient died after an illness of three months. Necropsy disclosed suppurating pancreatitis and marked degeneration of the peripheral nerves similar to that which occurs in cases of beriberi. An axonal type of reaction in the anterior horn cells and degeneration of the cells in the posterior root ganglions also were noted. There was no evidence of subacute combined degeneration.

The report of 2 cases by Dickey and McKinley [35] left no doubt that the clinical and pathologic picture of subacute combined degeneration of the type seen in pernicious anemia occurs in so-called prepernicious or preanemic pernicious anemia.

Neurologic changes commonly occur with pellagra, which is constantly being referred to as a cause of subacute combined degeneration of the spinal cord "like that seen with pernicious anemia," but one must be struck with the infrequency of the typical clinical or pathologic

34. Baló, Josef: Myelitis funicularis als Folgeerscheinung der Erkrankung des Pankreas, Deutsche Ztschr. f. Nervenh. **102**:275-286, 1928.

35. Dickey, L. B., and McKinley, J. C.: Subacute Combined Degeneration of the Spinal Cord Without Pernicious Anemia: Report of Two Cases with Autopsy Findings, Journal-Lancet **45**:331-334 (July 15) 1925.

picture of subacute combined degeneration in cases of pellagra. Tucker [36] reviewed the reports of 88 cases of pellagra in which there were neurologic findings. In 6 of these cases necropsy was performed. In an unpublished report we have reviewed 61 similar cases in 9 of which necropsy was performed. Neither of these reviews disclosed any clinical or pathologic evidence of the characteristic type of subacute combined degeneration seen in pernicious anemia, although neurologic findings of various kinds were commonly encountered. Some diffuse or focal degeneration of the fibers of the spinal cord has been reported in cases of pellagra,[37] but in only 1 case [38] were we able to find the familiar pathologic picture of subacute combined degeneration of the type seen in pernicious anemia, and in this report the results of gastric analysis and hematologic studies unfortunately had not been included. A spinal cord which was said to have come from a patient who had died of pellagra was sent to us from an anatomic laboratory, and examination revealed changes typical of those encountered in cases of pernicious anemia. Unfortunately, there was no clinical history in this case.

In scurvy the problem is somewhat different from that in pellagra. At least 1 of Nonne's [22] alcoholic patients (case 6) had scurvy, but pernicious anemia can hardly be excluded. Schlesinger [39] reported what appears to be a typical case in which the diagnosis was verified pathologically. In this case subacute combined degeneration of the spinal cord and marked degeneration of the peripheral nerves were associated with war edema and scurvy, but unfortunately, neither the results of gastric analysis nor the results of studies of the blood were included.

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36. Tucker, B. R.: The Neuropathology of Pellagra in Its Relation to the Cutaneous and Other Manifestations: A Preliminary Report, South. M. J. **28:** 603-606 (July) 1935.

37. Box, C. R.; Mott, F. W., and Sambon, L. W.: Pellagra in England: An Account of Four Recent Cases, with a Description of the Histological Changes in the Nervous System with an Account of the History and Natural History of the Disease, Brit. M. J. **2:**1-12 (July 5) 1913. Pentschew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis pellagrosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **118:**17-48, 1928. Spiller, W. G., and Anderson, P. V.: Pellagra with a Report of Two Cases with Necropsy, Am. J. M. Sc. **141:**94-106 (Jan.) 1911. Winkelman, N. W.: Beiträge zur Neurohistopathologie der Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102:**38-55, 1926.

38. Guillain, G.; Bertrand, I.; Mollaret, P., and Lereboullet, J.: Etude anatomique d'un cas français de pellagre avec paraplégie, Bull. et mém. Soc. méd. d. hôp. de Paris **50:**650-657 (May 11) 1934.

39. Schlesinger, Hermann: Erkrankungen des Nervensystems durch Nährschäden und Hunger, Ztschr. f. d. ges. Neurol. u. Psychiat. **59:**1-18, 1920.

The cases reported by Wohlwill [40] and by Modes [41] support the possibility that subacute combined degeneration of the type seen in pernicious anemia may be associated with scurvy, although pernicious anemia can hardly be said to have been excluded completely, even so far as this is possible, in these cases. The problem as it applies to sprue and allied conditions will be considered in detail later.

POISONING

The reactions of the nervous system to toxins differ considerably, but no case of poisoning could be found in which the clinical and pathologic pictures were indistinguishable from the neurologic picture seen in a case of well developed subacute combined degeneration of the type seen in pernicious anemia. In some of these cases, which have been well described by Davison and Keschner,[42] the reaction manifests itself as a striking degeneration of the peripheral fibers of the spinal cord.

Tuczek's [43] contributions are usually cited to prove that changes in the spinal cord, like those which occur in cases of pernicious anemia, may result from poisoning with ergot. The neurologic symptoms in the cases reported by Tuczek included chiefly psychoses, epileptiform attacks, choreiform movements, vertigo, scanning speech, paresthesias, Romberg's sign and loss of patellar tendon reflexes. The pathologic picture in the spinal cord resembled that of tabes dorsalis rather than that of subacute combined degeneration.

In Filimonoff's [44] case of poisoning by Lathyrus sativus the poisoning was complicated by senility and lymphatic leukemia. The neurologic symptoms of lathyrism are chiefly dysuria and spasticity. This is one ot the few instances in which necropsy has been performed in a case of lathyrism. The principal changes in the spinal cord included pial thickening, a nonareolar type of degeneration of the pyramidal tracts, some degeneration of the cerebellar tracts and sclerosis of the

40. Wohlwill, Friedrich: Zum Kapitel der pathologisch-anatomischen Veränderungen des Gehirns und Rückenmarks bei perniciöser Anämie und verwandten Affektionen. Deutsche Ztschr. f. Nervenh. **68-69**:438-480, 1921.

41. Modes, Ulrich: Zur Aetiologie der funikulären Spinalerkrankung, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:291-299, 1922.

42. Davison, Charles, and Keschner, Moses: Myelitic and Myelopathic Lesions: A Clinicopathologic Study; Toxic Myelonathy, Arch. Neurol. & Psychiat. **29**:600-614 (March) 1933.

43. Tuczek, Franz: Ueber die Veränderungen im Centralnervensystem, speciell in den Hintersträngen des Rückenmarks, bei Ergotismus, Arch. f. Psychiat. **13**:99-154, 1882; Ueber die bleibenden Folgen des Ergotismus für das Centralnervensystem, ibid. **18**:329-347, 1887.

44. Filimonoff, I. N.: Zur pathologisch-anatomischen Charakteristik des Lathyrismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:76-92, 1926.

vessels. Filimonoff placed particular emphasis on the occurrence of the degeneration of the pyramidal tracts.

An article by Oppenheim [45] often has been cited as proof that subacute combined degeneration, like the degeneration seen in pernicious anemia, may be caused by lead poisoning. The clinical diagnosis in the case which he reported had been multiple sclerosis. Necropsy revealed degeneration in Goll's tract, in the pyramidal tract, in the cerebellar tracts and in Clarke's column; an inflammatory reaction; an old infarction in the pons, and marked disease of the vessels. Oppenheim said he was undecided whether lead or syphilis was responsible for these changes and concluded that the lesions were certainly of vascular origin.

MISCELLANEOUS CAUSES

Grinker [31] has said: "It is rare to see a severe secondary anemia patient with a red blood cell count as low as the usual pernicious anemia without the presence of tingling and numbness, which usually are not associated with cord degeneration. These paresthesias caused by any type of anemia should be attributed to changes in the peripheral nerves." Bremer, on the other hand, stated the opinion that funicular degeneration probably underlies the paresthesias of pernicious anemia. It should be emphasized that the typical paresthesias of pernicious anemia are continuous and cannot be "rubbed away." It is unsafe to disregard the degeneration of the nerves, which has been described by Hamilton and Nixon, in cases of pernicious anemia as a possible source of the paresthesias in most instances; on the other hand, the frequency with which the same type of paresthesias ascend from the feet to encircle the lower part of the trunk to an indefinite level suggests that the changes in the spinal cord also may be capable of producing the paresthesias.

That secondary anemia alone causes persistent paresthesia or subacute combined degeneration of the spinal cord of the type seen in pernicious anemia can hardly be accepted as proved; clinical evidence alone seems to controvert this, as does the excellent study by Weil and Davison.[46] Not infrequently they observed that what clinically looked like subacute combined degeneration of the spinal cord in cases of secondary anemia turned out to be something entirely different pathologically.

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45. Oppenheim, Hermann: Zur Lehre von der multiplen Sklerose, Berl. klin. Wchnschr. **33**:184-189, 1896.

46. Weil, Arthur, and Davison, Charles: Changes in the Spinal Cord in Anemia: A Clinicomicroscopic Study, Arch. Neurol. & Psychiat. **22**:966-996 (Nov.) 1929.

Several cases in which amyotrophic lateral sclerosis was complicated by degeneration in the posterior funiculus have been described.[47] In the case reported by Stone in which there was typical pernicious anemia associated with atrophy of the small muscles of the hands, pathologic study verified the expected picture. In Hassin's report, in which there was no record of blood counts or gastric analysis, aseptic meningitis accompanied the amyotrophic lateral sclerosis. He explained the combination as the result of activity of one toxin, and he made the pertinent remark that combined sclerosis does not mean subacute combined degeneration. Viets,[48] in the discussion of Hassin's paper, emphasized the importance of insisting on good clinical evidence. Schaller [49] noted, as we also have, that liver therapy does not seem to help in cases of amyotrophic lateral sclerosis.

In many cases of infestation with Bothriocephalus [50] the typical clinical and pathologic picture of subacute combined degeneration of the type seen in pernicious anemia has been observed, yet one must be cautious in drawing the conclusion that this parasite is responsible for the typical lesion in the spinal cord, since proof consists of cure after removal of the parasite.

Infestation with Ancylostoma duodenale also has been regarded as a cause of subacute combined degeneration,[51] but the clinical picture in this case was unusual, and there was no report of a necropsy.

According to Keschner and Davison,[52] arteriosclerotic myelopathy is infrequent; it occurred only twice in 200 cases of cerebral arterio-

47. (*a*) Davison, Charles, and Wechsler, I. S.: Amyotrophic Lateral Sclerosis with Involvement of Posterior Column and Sensory Disturbances: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **35**:229-239 (Feb.) 1936. (*b*) Hassin, G. B.: Amyotrophic Lateral Sclerosis Complicated by Subacute Combined Degeneration of the Cord: Clinical and Pathologic Report of a Case, ibid. **29**:125-136 (Jan.) 1933. (*c*) Holmes, Gordon: A Case of Combined Degeneration of the Spinal Cord with Amyotrophy, Rev. Neurol. & Psychiat. **11**:76-88, 1913. (*d*) Nonne, M.: Rückenmarksuntersuchungen in Fällen von perniciöser Anämie, von Sepsis und von Senium, nebst Bemerkungen über Marchi-Veränderungen bei akute verlaufenden Rückenmarksprocessen, Deutsche Ztschr. f. Nervenh. **14**:192-241, 1899. (*e*) Stone, T. T.: Sub-Acute Combined Degeneration of the Spinal Cord with Chronic Changes in the Anterior Horns of the Cervico-Dorsal Region: A Histopathological Study, J. Nerv. & Ment. Dis. **73**:41-54 (Jan.) 1931.

48. Viets, H. R., in discussion on Hassin.[47b]

49. Schaller, Walter, in discussion on Hassin.[47b]

50. Naegeli: Ueber perniziöse Anämie, abstr., Klin. Wchnschr. **9**:1843-1844 (Sept. 27) 1930.

51. Early, P. V.: Subacute Combined Degeneration of the Cord Associated with Ankylostomum Duodenale and Achlorhydria, China M. J. **40**:465-466 (May) 1926.

52. Keschner, Moses, and Davison, Charles: Myelitic and Myelopathic Lesions: III. Arteriosclerotic and Arteritic Myelopathy, Arch. Neurol. & Psychiat. **29**:702-725 (April) 1933.

sclerosis. It appears as a patchy gliosis. In 1 of our cases, that of a man aged 70, there had been constant tingling of the hands and feet for three weeks, marked weakness and incoordination. Vibratory sensibility was absent over the iliac crests and malleoli; all tendon reflexes were absent, and the sphincters were paralyzed. Necropsy revealed gliosis in the posterior column of the spinal cord, degeneration of the periphery of the spinal cord without ballooning of the fibers or gliosis, degeneration of the roots of the spinal nerves and arteriosclerosis. Myelopathic lesions which are the result of arteritis are much more frequent than those which are the result of arteriosclerosis. In all the cases reported by Keschner and Davison the glial response was poor. Some writers have said that arteriosclerotic changes are common in the spinal cord.

Nonne,[47d] in a study of 10 senile patients, observed that the associated changes in the spinal cord did not evince themselves through any particular neurologic signs. In these 10 cases there was an increase of neuroglia, and there often was simple atrophy of nerve fibers in the periphery of the spinal cord, without inflammation and independent of sclerosis of the vessels. Diminution of vibratory sensibility is common among patients who are beyond the fifth decade of life, and this must be considered in deciding to what extent impairment in vibratory sensibility may be utilized in the diagnosis of subacute combined degeneration in cases of pernicious anemia. In 1 of our cases, that of a man aged 70 who had pernicious anemia and a loss of vibratory sensation over the iliac crests and the malleoli, necropsy disclosed marked thinning of the fibers of the anterior and posterior roots of the spinal nerves but did not disclose anything to suggest subacute combined degeneration of the spinal cord. According to Pearson,[53] impairment of vibratory sensibility among elderly persons is the result of arteriosclerotic circulatory impairment in the thoracic segment of Goll's tract.

Curschmann,[54] who had stated that he doubted the existence of subacute combined degeneration with anything but pernicious anemia, reversed his opinion on the basis of clinical findings, which were not altogether typical, in a case of hemolytic icterus. Necropsy was not performed in this case. Delbeke and Van Bogaert,[55] however, reported a case in which necropsy revealed changes in the spinal cord that were

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53. Pearson, G. H. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482-496 (Sept.) 1928.

54. Curschmann, Hans: Ueber funikuläre Myelose bei hämolytischem Ikterus, Deutsche Ztschr. f. Nervenh. **122**:119-125, 1931.

55. Delbeke, R., and Van Bogaert, L.: Les myélites funiculaires en dehors de l'anémia pernicieuse: II. Une paraplégie à type de compression au cours d'un ictére hémolytique, Ann. de méd. **34**:382-397 (Nov.) 1933.

like those noted in cases of pernicious anemia. The spinal fluid contained an increased amount of albumin, and there was mild pleocytosis. The value for the hemoglobin in the blood was 70 per cent, and there were 2,900,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded.

Hemorrhagic and infiltrative lesions of the nervous system are fairly common in leukemia, occurring in 20.5 per cent of cases.[56] Such lesions are in keeping with this disease, but that changes which are "just like those of pernicious anemia" should occur in the spinal cord in cases of leukemia is not altogether what might be expected. One or the other of Schultze's [57] contributions is usually quoted as authority for the occurrence of such lesions in cases of leukemia. The more recent reference is to a twelve line discussion in which Schultze referred to the earlier publication. In this admirably clear and concise article he described the occurrence of swollen and partly degenerated axis-cylinders, singly and in groups, three to twenty to the cross-section, in all columns of the spinal cord, especially in the lateral columns. These changes, he said, may be seen also in cases of nephritis, being observed near the periphery of the lateral columns. There was no trace of leukocytic or hemorrhagic infiltration.

Pernicious anemia of pregnancy seems to offer a hopeful field for the discovery of a typical example of subacute combined degeneration, like that which occurs in cases of pernicious anemia. Naegeli said that glossitis, achylia and degeneration of the spinal cord do occur in cases of pernicious anemia of pregnancy, but Filo [58] said that neurologic changes are rare in such cases. The time factor may not permit the complete development of subacute combined degeneration. Myelitis of pregnancy [59] must not be confused with subacute combined degeneration, although in cases of myelitis the history may be strongly suggestive of typical combined degeneration of the spinal cord.[60] Hassin and Ettleson [61] gave an excellent description of the pathologic changes

56. Schwab, R. S., and Weiss, Soma: The Neurologic Aspect of Leukemia, Am. J. M. Sc. **189**:766-778 (June) 1935.

57. Schultze, Friedrich: I. Ueber das Vorkommen gequollener Axencylinder im Rückenmarke, Neurol. Centralbl. **3**:193-195 (May) 1884; Historische Notiz über Degenerationsherde in der weissen Substanz bei Leukämie und über Degenerationen im Rückenmark bei Zehrkrankheiten, Deutsche Ztschr. f. Nervenh. **11**: 162-163, 1897.

58. Filo, Emanuel: Ueber die Schwangerschaftsperniziosa, Folia haemat. **44**: 446-474, 1931.

59. Rosenberg, F., and Schmincke, A.: Zur Pathologie der toxischen Graviditätsmyelitis, Virchows Arch. f. path. Anat. **184**:329-345, 1906.

60. Spitzer, Walther: Myelitis und Rückenmarksläsion in ihren Beziehungen zu Schwangerschaft und Geburt, Arch. f. Gynäk. **152**:517-528, 1933.

61. Hassin, G. B., and Ettleson, Abraham: Paraplegia of Pregnancy (Subacute Combined Degeneration of the Cord), Arch. Neurol. & Psychiat. **32**:1273-1281 (Dec.) 1934.

that occurred in a case in which they classified the disorder as due to subacute combined degeneration of the spinal cord associated with pregnancy. The authors said that the changes noted "were degenerative, of the type observed in subacute combined degeneration of the spinal cord; they resembled nothing else." Unfortunately, in this case the subacute combined degeneration was not uncomplicated. The patient was a girl aged 19 years who had had gonorrhea and syphilis. Paraplegia and urinary incontinence had occurred three days after an attack of pharyngitis; later blood culture revealed the presence of staphylococci. Necropsy disclosed multiple abscesses of the viscera and marked degeneration of the lateral columns of the spinal cord. The degeneration was less marked in the anterior columns than it was in the lateral columns, and the degenerative changes were slight in the posterior columns. There was axonal degeneration of the ganglion cells, and the blood vessels and meninges were markedly infiltrated with lymphocytes and polymorphonuclear leukocytes. In another case, which was reported by Hassin and Stone,[62] the illness began two weeks post partum. The symptoms become progressively worse; three years after the onset of the illness the lower extremities became markedly adducted and flexed. Examination revealed complete spinal subarachnoid block. Laminectomy was performed, and a large blood clot was removed. Necropsy was limited to a part of the cord. The results of gastric analysis were not mentioned.

Kahler and Pick [63] gave one of the earliest descriptions of subacute combined degeneration, probably of the so-called primary type. In 1 of our cases in which the disability began early in childhood and was progressive, the combined sclerosis was marked by complete absence of any sievelike appearance in the spinal cord and by an extraordinarily dense net work of glial fibers.

A number of unclassified diseases remain in which subacute combined degeneration has been mentioned as a complication of interest. Anemia was said to have been absent in a case [64] in which the disease clinically and pathologically resembled the subacute combined degeneration of pernicious anemia. The value for hemoglobin was 80 per cent, and there were 3,600,000 erythrocytes per cubic millimeter of blood. Examination of blood smears did not reveal any abnormality. The patient had had attacks of diarrhea. The results of gastric analysis

62. Hassin, G. B., and Stone, T. T.: Subacute Combined Degeneration of the Spinal Cord: Report of a Case Following Childbirth and Complicated by Spinal Epidural Hemorrhage, Arch. Neurol. & Psychiat. **34**:401-406 (Aug.) 1935.

63. Kahler, Otto, and Pick, Arnold: Ueber combinierte Systemerkrankungen des Rückenmarkes, Arch. f. Psychiat. **8**:251-282, 1878.

64. Schaeffer, Henri, and Vialard: Sclérose combinée subaiguë de la moelle sans anémie, Paris méd. **2**:301-305 (Oct. 5) 1929.

were not reported. In another case,[65] which was reported as a case of subacute combined sclerosis without anemia or cachexia, the signs pointed to involvement of the posterior columns and the extrapyramidal system; however, the rigidity was interpreted as originating in the pyramidal tracts. Free hydrochloric acid was absent from the gastric juice; there was no necropsy.

Delhaye and Van Bogaert[66] reported a case of subacute combined degeneration associated with widespread cellular changes in the nervous system. The patient was a man aged 60 who was deaf and had sphincteral disturbances. Babinski reflexes were present. The skin was bronzed, and the patient was emaciated. The value for the hemoglobin was 90 per cent, and there were 3,300,000 erythrocytes per cubic millimeter of blood. There were some myelocytes in the blood. In addition to the changes in the spinal cord, necropsy revealed arteriosclerosis, enlargement of the liver and spleen, perivascular lymphocytic infiltration of the skin, periportal cirrhosis, cortical sclerosis of the adrenal glands, hyperplasia of other parts of the chromaffin system and some changes in the hypophysis cerebri. The disease was classified as a mixed endocrine disorder with lesions in the adrenal glands, the afferent chromaffin system and the hypophysis cerebri.

In the unusual case reported by Sjögren and Wohlfahrt[67] both the clinical and the neuropathologic picture were those of subacute combined degeneration of the type seen in pernicious anemia. The patient was cachetic, and Bence-Jones' protein was present in the urine. The value for hemoglobin was 67 per cent, and there were 2,900,000 erythrocytes per cubic millimeter of blood. The results of gastric analysis were not recorded, and the diagnosis remained in doubt.

Bodechtel,[68] in his excellent article on funicular spinal disease, showed sections of the spinal cord; in at least four illustrations the changes strongly resembled those of pernicious anemia. The author simply said that these spinal cords were not from patients with pernicious anemia; he did not give any further data. In another case of subacute combined degeneration the presence of dementia paralytica had not been suspected until the blood and sections of the brain were studied.

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65. Thomas, André; Schaeffer, H., and Amyot, R.: Sclérose combinée subaiguë de la moelle sans anémie, in cachexie, Rev. neurol. **2**:561-567 (Nov.) 1929.

66. Delhaye, A., and Van Bogaert, L.: Les myélites funiculaires en dehors de l'anémie pernicieuse: I. Une paraplégie en flexion au cours d'un syndrome endocrinien et hépatique avec mélano-épidermie, Ann. de méd. **34**:42-68 (June) 1933.

67. Sjögren, V. H., and Wohlfahrt, S.: Ein Symptomenkomplex; funikuläre Spinalerkrankung sowie Bence Jones' Eiweisskörper im Harn: I. Klinische und anatomische Befunde, Acta psychiat. et neurol. **8**:253-260, 1933.

68. Bodechtel, G.: Zur Histopathologie der funikulären Spinalerkrankung mit besonderer Berücksichtigung der bei der perniciösen Anämie zu sehenden Grosshirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**:104-167, 1931.

The funiculi of the spinal cord may be altered by many diseases and in many ways. The differential diagnosis cannot always be made on clinical evidence alone. Before the cause of subacute combined degeneration of the spinal cord like that which occurs in cases of pernicious anemia can rightly be determined, typical and well developed clinical and pathologic signs and symptoms must be brought forward as evidence. On the basis of a survey of the important available literature, it appears that this familiar and challenging picture may be brought about by chronic alcoholism, gastric carcinoma, obstruction and fistulas of the intestinal tract, pernicious anemia, so-called prepernicious anemia and scurvy (this may have been a complication). It possibly may be similarly related to pancreatitis, pellagra and hemolytic icterus, and it has been in some manner associated with amyotrophic lateral sclerosis and a number of unclassified diseases.

An important physiologic principle appears to be involved. Careful hematologic studies, gastric analysis and an investigation of the presence of Castle's intrinsic factor, if facilities are available, possibly would lead to the disclosure of some one underlying cause, probably nutritional and in the nature of a deficiency.

A CLINICAL REVIEW OF CASES IN WHICH A DIAGNOSIS OF COMBINED SCLEROSIS WAS MADE

In reviewing our group of approximately 2,000 cases in which the disease was classified as subacute combined degeneration of the spinal cord, we excluded all cases in which gastric analysis revealed absence of free hydrochloric acid (fig. 1). Thus most, if not all, cases of pernicious anemia were eliminated. The insert, for purpose of comparison, represents the findings noted in pernicious anemia, expressed in percentage of cases. We should like to draw attention to the frequency of the paresthesias and to the relative prominence of involvement of the posterior columns as compared with involvement of the lateral columns and to suggest a comparison of the entire insert with other figures in the illustration.

In the first group of cases we classified the combined sclerosis rightly or wrongly as arteriosclerotic or senile. In this group of cases the paresthesias were usually transitory and otherwise not typical of those seen with pernicious anemia. Complications of various kinds, as might be expected among patients of the same age, were common but could not safely be regarded as causes.

In the group in which the diagnosis was questionable there was usually a suggestion of trauma, infection or multiple sclerosis, but the objective findings were those of combined involvement. In the case which was said to illustrate the type of degeneration seen in pernicious

anemia, the diagnosis was complicated by the possibility of superimposed arsenical neuritis and by predominant unilateral spasticity. In 1 case in this group there was an obstruction in the first part of the duodenum and Korsakoff's psychosis, in another case myxedema and in another postural hypotension. Several of the cases in this group might have been included in the group of cases in which arteriosclerosis was present.

We do not mean to imply that subacute combined degeneration and multiple sclerosis are in any way related, but the differential diagnosis

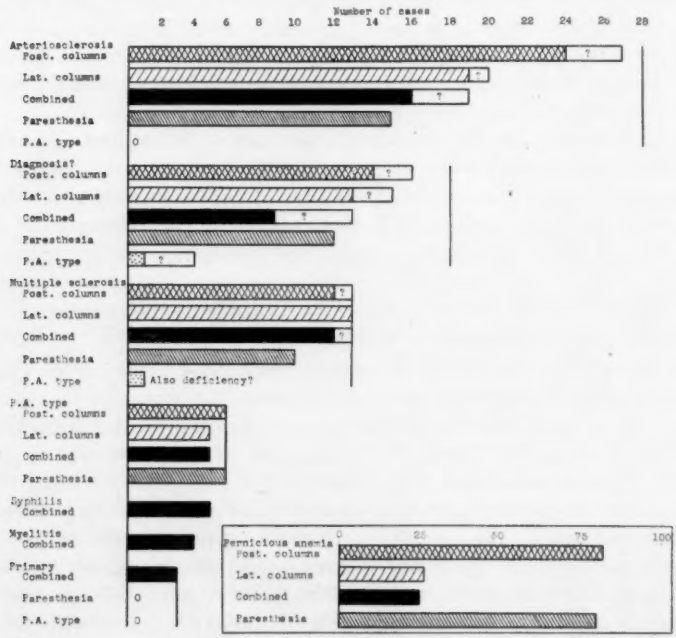

Fig. 1.—Groups of cases in which there were signs of involvement of the posterior and lateral columns of the spinal cord. *Post.* indicates posterior; *Lat.*, lateral; *P. A.*, pernicious anemia.

may be difficult in early stages. In 1 case we classified the condition as combined sclerosis associated with severe and chronic infection of the nasal sinuses after examination in 1922. Seven years later necropsy disclosed typical multiple sclerosis. In 1 of the cases of multiple sclerosis the history of diarrhea, vomiting and "sore mouth" suggested an associated dietary deficiency. The diagnosis of multiple sclerosis in the cases in this group was determined largely on the basis of the previous or subsequent history or on the basis of findings obtained by examination of the spinal fluid.

There were 6 cases of subacute combined degeneration of the type seen in pernicious anemia which, in view of the presence of free hydrochloric acid in the gastric juice, we could not classify as cases of pernicious anemia. Fortunately, we made lumbar punctures in 2 of these cases, but unfortunately this was not done in the other cases. Examination of the spinal fluid suggested the possibility of meningoradiculomyelitis in 1 case and multiple sclerosis in the other. In the first case "stomach trouble" had been present for fifteen years, and roentgenologic examination revealed the presence of a duodenal ulcer. In the third case the patient became depressed after the death of his wife, refused to eat and lost 50 pounds (22.7 Kg.) but improved promptly as a result of liver therapy. He had also postural hypotension, which is not infrequently associated with neurologic signs suggestive of subacute combined degeneration or multiple sclerosis. In the fourth case there was associated glossitis. The fifth case was that of a man aged 49 who, according to his physician, "became rigid as a board before he died." The physician of the sixth patient informed us seven years after we had seen the patient that the value for hemoglobin was 82 per cent, that there were 3,610,000 erythrocytes per cubic millimeter of blood and that macrocytes occasionally were noted in blood smears. The patient had been taking liver since she left the clinic, with the exception of the eight months that preceded the writing of the physician's letter. Her neurologic condition had become only slightly worse than it had been.

A case not included in this group illustrates the value of lumbar puncture when the diagnosis is doubtful.

The patient was a physician aged 62. Five months before he came to the clinic persistent tingling had developed in his feet, which had also become somewhat ataxic. There had not been any paresthesia of the fingers. Objective examination disclosed a moderate impairment of vibratory sensibility over the malleoli, absence of vibratory sensibility over the iliac crests, slight impairment of superficial and postural sensibility in the toes and slight Babinski reflexes. The tentative diagnosis was subacute combined degeneration of the spinal cord, but the hematologic picture was entirely normal, and free hydrochloric acid was present in the stomach. Lumbar puncture disclosed complete spinal subarachnoid block by jugular compression tests; there was 110 mg. of protein per hundred cubic centimeters of spinal fluid. Iodized poppy-seed oil 40 per cent was injected into the spinal canal for the purpose of localization. Exploration revealed dense adhesive arachnoiditis at the level of the eleventh thoracic vertebra. Only then did the patient recall that while he had been casting for trout some months before the onset of his disability he had fallen 20 feet (6 meters) down a bank and had injured his back.

In the cases of syphilis, myelitis and primary degeneration of the central nervous system there was no evidence of subacute combined degeneration of the type seen in pernicious anemia.

To summarize, we have observed 77 cases in which there were signs of involvement of the posterior and lateral columns of the spinal cord and in which free hydrochloric acid was present in the gastric contents. The latter finding practically eliminates pernicious anemia as a cause of the involvement. When we add gradually developing, symmetrical, persistent paresthesias of the hands and feet, the clinical neurologic picture becomes that seen typically in cases of pernicious anemia. There were 8 cases in which these symptoms were present; in 3 of these there was no reason for believing that a nutritional factor entered into the cause; in the remaining 5 there was reason for thinking so, although we do not venture to say that the pathologic examination in these cases would have disclosed classic subacute combined degeneration of the spinal cord. To borrow a term from the serologic laboratory, occasional "false positive results," which are indistinguishable clinically at a given time from the picture typically seen with pernicious anemia, may be met. In cases in which the diagnosis is doubtful an examination of the spinal fluid increases the accuracy of the diagnosis. In none of these could the exact pathologic nature of the lesion in the cord be verified.

SPRUE AND ALLIED CONDITIONS

Sprue and allied conditions deserve special attention. In a review of more than two hundred available articles on the subject of sprue it was found that only twenty included evidence of organic involvement of the nervous system (table 2).[69]

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69. (*a*) Baumgartner, E. A., and Thomas, W. S.: A Case of Tropical Sprue with Autopsy, Clifton M. Bull. **11**:90-93, 1925. (*b*) Elders, C.: Tropical Sprue and Pernicious Anaemia: Aetiology and Treatment, Lancet **1**:75-77 (Jan. 10) 1925. (*c*) Reed, A. C., and Wyckoff, H. A.: The Common Picture of Sprue, Pernicious Anemia, and Combined Degeneration, Am. J. Trop. Med. **6**:221-237 (May) 1926. (*d*) Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med. **40**:203-215 (Aug.) 1927. (*e*) Holst, J. E.: Ein in Dänemark aufgetretener Fall von Sprue, Acta med. Scandinav. **66**:74-99, 1927. (*f*) Graves, M. L., in discussion on Wood.[72b] (*g*) Korsberg, Axel, quoted by Holst.[69e] (*h*) Brøns, J., quoted by Holst.[69e] (*i*) Low, G. C., and Benton, D.: Sprue in Natives, J. Trop. Med. **30**:193 (Aug. 2) 1927. (*j*) Reed, A. C., and Ash, J. E.: Atypical Sprue, Arch. Int. Med. **40**:786-799 (Dec.) 1927. (*k*) Baumgartner, E. A.: Parathyroid in the Treatment of Tropical Sprue, Am. J. Trop. Med. **7**:181-191 (May) 1927. (*l*) Antoine, Edouard: Trois cas de diarrhée grave à allure de sprue; étude de cette affection tropicale, Arch. d. mal. de l'app. digestif **18**:45-65 (Jan.) 1928. (*m*) Richardson, Wyman, and Klumpp, T. G.: Sprue: Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, New England J. Med. **199**:215-218 (Aug. 2) 1928. (*n*) Thaysen, T. E. H.: Diskussion: Die Symptomatologie der nicht tropischen Sprue, Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **8**:152-155, 1928. (*o*) Zadek, Ernst: Ueber Sprue, Med. Klin. **24**:776-777 (May 18) 1928. (*p*)

Ashford [69r] gave an excellent summary of the general clinical picture. Regarding the symptoms which are referable to the spinal cord he said:

> This syndrome is extremely rare in sprue. With exceptions noted, numbness in the extremities and tetanoid cramps in muscles of leg (half of the writer's cases and otherwise explained), the symptoms relative to cord lesions are not characteristic of sprue.
>
> Insomnia, sluggish or abolished knee reflexes, nervous depression and irritability, vague muscle pains, palpitation of the heart, loss of memory, and weight over the cerebellum are frequent in the latter disease, but headache and dizziness are not common. That the central nervous system is not organically affected, as a rule, and that these symptoms are functional due to disordered nutrition is seen in their prompt dissipation by an adequate sprue diet, perhaps reënforced by calcium therapy and parathyroid extract subcutaneously administered. Only rarely are definite lesions of the cord evidenced in sprue and then they are almost always slight and ephemeral when a proper diet is applied.

Fairley [70] said: "I have never observed subacute combined degeneration in sprue, though neuritic manifestations are common enough."

The mental state in cases of sprue is usually one of depression.[71] The patient reported on by Suárez lost his ideas of persecution and

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Holmes, W. H., and Starr, Paul: A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue; Emaciation, Anemia, Tetany, Chronic Diarrhea and Malabsorption of Fat, J. A. M. A. **92**:975-980 (March 23) 1929. (*q*) Hance, J. B.: Notes on the Pathogenesis of Sprue and the Asthenic Diarrhoea of Indians, with Special Reference to the Rôle Played Therein by Amoebiasis: The Probable Identity of the Two Former Conditions, and Their Connection with Addisonian Anaemia—Subacute Combined Degeneration of the Cord—Hunterian Glossitis Syndrome of Hurst, Indian M. Gaz. **65**:125-130 (March) 1930. (*r*) Ashford, B. K.: The Differential Diagnosis of Sprue and Pernicious Anemia, Am. J. Trop. Med. **12**:199-215 (May) 1932. (*s*) Keefer, C. S.; Yang, C. S., and Huang, K. K.: Anemia Associated with Chronic Dysentery: Clinical Considerations, with Special Reference to the Cause and Treatment, Arch. Int. Med. **47**:436-466 (March) 1931. (*t*) Suárez, Jenaro: Pernicious Anemia and Sprue, Porto Rico J. Pub. Health & Trop. Med. **7**:145-165 (Dec.) 1931. (*u*) Brown, Madelaine R.: The Pathology of the Gastro-Intestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord: Study of One Hundred and Fifty-One Autopsies, New England J. Med. **210**:473-477 (March 1) 1934. (*v*) Thaysen, T. E. H.: La stéatorrhée idiopathique, la sprue tropicale et non tropicale et l'infantilisme intestinal, Arch. d. mal. de l'app. digestif **24**:123-169 (Feb.) 1934. (*w*) Castle, W. B.; Rhoads, C. P.; Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and Subsequent Experiments on Animals, Arch. Int. Med. **56**:627-699 (Oct.) 1935.

70. Fairley, N. H.: Tropical Sprue and Its Modern Treatment, Brit. M. J. **2**: 1192-1194 (Dec. 29) 1934.

71. Ashford, B. K.: A Case of Hypoplastic Anemia, Pernicious Type, in the Course of Sprue, with Frequently Repeated Hematological Examinations, Porto Rico J. Pub. Health & Trop. Med. **7**:11-22 (Sept.) 1931. Baumgartner and Smith.[69d] Campbell, R. D.: Sprue in Southwest Virginia: A Case Report, Virginia M. Monthly **58**:380-382 (Sept.) 1931. Malcolmson, G. E., and Murphy, K. N.: The Frequency of Sprue Among Indians in Madras, Indian M. Gaz. **66**: 192-193 (April) 1931.

TABLE 2.—*Principal Neurologic Features Noted in Cases of Sprue and Allied Conditions Reported*

Year	Author	Paresthesia		Reflexes			Sensation		Comments
		Hands	Feet	Patellar	Achilles Tendon	Babinski	Vibratory	Joint	
1925	Baumgartner and Thomas [69a]	+	+	Diminished, grade 2	..	..	..	..	Question of slight degeneration of cervical portion of spinal cord at necropsy
1925	Elders [69b]	..	..	..	..	..	..	..	Ataxia; anesthesia of legs
1926	Reed and Wyckoff [69c]	..	..	Absent	Absent	..	..	..	
	Reed and Wyckoff	+	+	..	..	..	..	..	Clumsiness of hands
	Reed and Wyckoff	+	+	..	..	..	..	..	
1927	Baumgartner and Smith [69d]	..	..	..	..	..	..	..	Numbness and tingling in 8 to 15 cases
1927	Holst [69e]	Normal	Normal	Increased	+	+	..	..	Spastic paraplegia
	Graves [69f]	..	..	..	..	..	..	..	Patient 9 years of age; epileptoid syndrome
	Korsberg [69g]	..	..	Absent	..	..	..	..	Paresis of legs and sphincters
	Brøns [69h]	..	..	..	..	..	..	..	Polyneuritis
1927	Low and Benton [69i]	..	..	Absent	..	..	..	..	Irritability
1927	Reed and Ash [69j] (case 1)	+	+	..	..	..	..	..	Negative results of necropsy
	Reed and Ash (case 3)?	+	+	..	..	..	..	..	No free hydrochloric acid in stomach; necropsy revealed combined degeneration
	Reed and Ash (case 4)?	..	..	..	..	..	..	..	No free hydrochloric acid in stomach; marked combined sclerosis; necropsy revealed combined degeneration
	Reed and Ash (case 8)?	..	..	..	..	..	..	..	Neuritis of both brachial plexuses; no test meal given
1927	Baumgartner [69k]	..	..	Absent	..	..	Slight decrease	..	Left patellar reflex normal
1928	Antoine [69l] (case 3)	+	+	..	..	..	..	..	
1928	Richardson and Klumpp [69m]	+	+	Absent	Absent	..	..	..	Transitory paresthesias; slight ataxia
1928	Thaysen [69n]	..	..	..	..	±	..	..	Two cases; one patient could scarcely walk
1928	Zadek [69o]	..	..	Absent	Absent	..	..	..	
1929	Holmes and Starr [69p] (case 2)	+	+	..	..	..	..	..	
	Holmes and Starr (case 5)	..	+	..	..	..	..	..	
1930	Hance [69q]	..	..	..	..	..	..	..	Total of 26 cases: 20 of sprue, 3 of combined degeneration, 3 of pernicious anemia; 5 with paresthesia; 2 with ataxia (groups not stated)
1931	Ashford [69r] (case 59)	..	+	..	..	..	..	..	Loss of memory; despondency
1931	Keefer, Yang and Huang [69s]	..	..	Absent	Absent	..	Absent	Absent	Ataxia
	Keefer, Yang and Huang	..	..	..	..	..	..	..	Peripheral neuritis
	Keefer, Yang and Huang	..	..	..	..	..	..	..	Combined degeneration
1931	Suárez [69t] (case 21320)	..	..	Absent	Absent	..	..	..	All reflexes ?
1934	Brown [69u]	..	..	..	..	..	..	..	One patient had free hydrochloric acid in stomach; pernicious anemia; degeneration of cord (necropsy report)
1934	Thaysen [69v]	..	..	..	..	+	..	..	Patient disappeared
1935	Castle, Rhoads, Lawson and Payne [69w]	±	±	Decreased in 3 cases			All decreased	..	Total of 92 cases; changes in central nervous system in 8; in 3 of 8 cases gastric acidity not reported; in 3, no free hydrochloric acid in stomach; in 2 acid was found; disturbance of locomotion

hallucinations after treatment with liver had been instituted. Epileptoid and epileptiform convulsions and petit mal also have been observed.[72]

Gastric analysis revealed the presence of free hydrochloric acid in 52 of the 93 cases of sprue and related conditions which have been observed at the clinic. The presence of free hydrochloric acid was regarded as presumptive evidence that no cases of pernicious anemia were included in this study. Neurologic examination was performed in 29 of the 52 cases.

The findings in 11 of these 29 cases are shown in table 3. In 6 of these cases there had been continuous paresthesias of the hands and

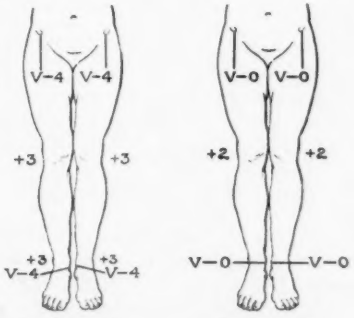

Fig. 2.—Nontropical sprue in a man aged 26. Subacute combined degeneration of the spinal cord, with improvement resulting from intramuscular injection of liver extract. *A*, March 6, 1934. For ten years the patient had had remitting attacks of watery diarrhea, abdominal pain, gas and bloating. Glossitis was noted two years previously. Paresthesia of the hands had been present for two months and paresthesia of the feet for one and one-half months. Astereognosis had developed. A histamine meal test showed free hydrochloric acid of 86. Hemoglobin, 10.4 Gm.; erythrocytes, 2,580,000; macrocytic hyperchromic morphologic picture. On April 16, 1934, the paresthesia was improved. Vibration, —2; joint sensibility, —1; Babinski reflex, +2. On July 10, 1934, there was transitory paresthesia of the fingers. Vibration over the iliac crests, 0; over the malleoli, —2; joint sensibility, 0; Babinski reflex, +1; hemoglobin, 12.9 Gm.; erythrocytes, 4,320,000; normal morphologic picture; absence of usual markings of small intestine; hypomotility. On July 8, 1935: hemoglobin, 10.5 Gm.; erythrocytes, 3,960,000; moderate hypochromic, normocytic blood picture. *B*, April 22, 1936: general health only fair, some diarrhea, no glossitis, normal reaction of pupils to light; no injection of liver extract for past five months.

72. (*a*) Ashford, B. K.: The Relation of Monilia Psilosis to Tropical Sprue and an Evaluation of Fermentation of Sugar as a Criterion for Specificity, Porto Rico J. Pub. Health and Trop. Med. **6**:310-333 (March) 1931. (*b*) Wood, E. J.: The Recognition of Tropical Sprue in the United States, J. A. M. A. **73**:165-167 (July 19) 1919. (*c*) Holst.[69e]

feet; in 6 cases the tendon reflexes were diminished or absent and in 1 case they were increased; in 10 cases vibratory sensibility was impaired or absent, usually at both iliac crests and at the malleoli. Macrocytosis was present in 8 cases. We regard the neurologic condition in case 12 as a complication not directly related to sprue.

Case 7 is of sufficient significance to warrant a more detailed report (fig. 2).

TABLE 3.—*Summary of Data in Twelve Cases of Sprue and Related Conditions in Which Neurologic Examination Was Performed and Free Hydrochloric Acid Was Present*

				Paresthesia*		Reflexes, Grade†			Sensation†			
Case	Sex	Age, Years	Residence	Hands	Feet	Patellar	Achilles Tendon	Babinski	Vibratory	Joint	Hydrochloric Acid in Gastric Juice‡	Macrocytosis
1	M	52	Indiana	..	..	...	...	...	0 −3	...	16	0
2§	M	63	North India	6	4	...	...	...	−4 −4	...	22	+
3	F	53	Manila	12	12	...	...	...	0 −3 −4	... −2	66	+
4	M	65	Kentucky	..	..	...	...	...	0 −2	...	50	+
5	M	44	Illinois	..	..	−4	...	...	...	...	58	0
6‖	M	44	Washington	12	60	−4	−4	...	0 −2 −3	... −2	38	+
7	M	26	Nebraska	2	1½	+3	+3	+3	−4 −4	... −2	86	+
8	M	54	Illinois	36	36	−2	−4	+1?	0 −2	...	34	+
9	M	56	Central America	..	..	−4	−4	...	−2 −2	...	10	+
10	M	43	Illinois	42	42	−4	−4	...	−4 −4	... −2	18	0
11	M	54	West Indies	..	..	...	−2	...	−4 −4	...	20	+
12	M	30	Ohio	Palsy of left peroneal nerve¶							24	0

* Duration in months; transitory paresthesia not included.

† 0 represents normal. Normal responses are not charted except under vibration, when upper figure represents vibratory sensation over crests of ilium and lower figure represents vibratory sensation over malleoli; −4 indicates absence of reflex.

‡ Determined according to method of Töpfer.

§ Rectal sphincter, −2.

‖ Paresis of hands and feet, +3.

¶ Presumably the palsy was caused by pressure and was not specifically related to nontropical sprue.

A Jew aged 26 first came to the clinic on March 3, 1934. While in high school he had gone through about twelve periods of weakness, anorexia, loss of weight, pallor and vague abdominal distress. These attacks had not caused him to miss school. He entered college at the age of 17, when he again had gastrointestinal symptoms of the same type. There were periods of constipation alternating with periods of diarrhea. The stools were loose and watery but did not contain mucus or blood. Because of these symptoms he was forced to dis-

continue college for two and a half years. During this period his appendix and tonsils were removed. In 1929 he returned to college, continued his work for three years and was graduated with honors. The symptoms had returned but, in addition, he had diarrhea and a sore mouth. Orange juice had been taken faithfully. After he completed his college work he never was strong enough to do much work. During the winter previous to his admission to the clinic the gastro-intestinal disturbance returned. Two months before he came to the clinic, tingling developed in the fingers; this spread and gradually involved the whole hand. He was unable to take money out of his pocket and had difficulty in buttoning his clothes because of this disturbance. Shortly after the onset of paresthesia in the fingers, tingling developed in the toes. He became irritable and depressed. His best weight had been 115 pounds (52.6 Kg.) when he was fully dressed; he weighed only 90 pounds (40.8 Kg.) when he came to the clinic.

General physical examination revealed a marked loss of weight, pallor, a smooth tongue, some reddened areas on the gums and some clubbing of the fingers. Moderate edema was present in the lower extremities. The essential laboratory findings were as follows: The concentration of hemoglobin was 10.3 Gm. per hundred cubic centimeters of blood. The erythrocytes numbered 2,580,000 and the leukocytes 2,700 per cubic millimeter of blood. A differential blood count revealed that there were 30 per cent lymphocytes, 6.5 per cent monocytes and 63.5 per cent polymorphonuclear neutrophils. Morphologic examination of the blood smears showed marked macrocytosis and revealed that the erythrocytes were well filled with hemoglobin. There was little increased lobulation of the nucleus in the polymorphonuclear neutrophils. Howell-Jolly bodies and basophilic stippling were present. Gastric analysis after ingestion of ordinary cookie meal revealed that the value for the total gastric acidity was 38 and that for the free hydrochloric acid was 22, according to the method of Töpfer. After the injection of histamine, values as high as 86 were obtained for free hydrochloric acid. The function of the liver was normal, as determined by the dye retention test. The volume index was 1.22. Roentgenoscopic examination of the small bowel showed some dilatation and hypomotility. The percentage of reticulated erythrocytes was from 1 to 2 before the institution of treatment. On March 11 a high calorie-high vitamin diet which was low in fat was prescribed, and in addition the patient was given five successive injections of 3 cc. of liver extract. Weekly injections of liver extract were given thereafter. On March 18 the percentage of reticulated erythrocytes was 11.8. The patient had gained markedly in weight and strength, and when he was seen again, on July 9, the concentration of hemoglobin was 12.9 Gm. per hundred cubic centimeters of blood and the erythrocytes numbered 4,320,000 and the leukocytes 5,100 per cubic millimeter of blood. Morphologically, the erythrocytes were normal in appearance.

The patient was again seen in July 1935, because of a recurrence of symptoms. At this time the concentration of hemoglobin was 10.5 Gm. per hundred cubic centimeters of blood, the erythrocyte count was 3,960,000 and the leukocyte count was 3,500. No macrocytosis could be demonstrated. There was moderate hypochromasia in the erythrocytes. At this time, in addition to the liver extract, he was given 1 Gm. of iron daily in the form of ferrous carbonate.

The outstanding neurologic findings on March 6, 1934, included diminution of the pupillary response to light. The reaction to convergence was normal. The patellar and achilles tendon reflexes were disproportionately active. The abdominal reflexes were absent. The Babinski, Chaddock, Rossolimo and Mendel-Bechterew reflexes were strongly pathologic bilaterally. There was definite inco-

ordination of the upper extremities, as tested with the finger to nose test. A moderate grade of astereognosis was present. Vibratory sensibility was absent over the iliac crest and lower extremities. Appreciation of movement of the joints was markedly impaired in the toes. There was slight disturbance of tactile sensibility over the toes. The diagnosis was subacute combined degeneration of the spinal cord associated with degeneration of the peripheral nerves. The neurologic examination was repeated on April 16, after the patient had undergone treatment for one month. He said he felt little better than he had at the time of the previous neurologic examination. The findings were essentially the same as they had been before, except that the Babinski and Chaddock reflexes were less marked than they had been previously. The Rossolimo and Mendel-Bechterew reflexes were no longer obtainable. Vibratory sensibility had improved somewhat, and the patient was able to feel the vibrations of the fork moderately well when it was placed over the iliac crest. The vibration could not be felt when the fork was placed over the malleoli of the right lower extremity, and vibratory sensation was moderately impaired when the fork was placed over the malleoli of the left lower extremity. Joint sensibility of the toes was only slightly impaired. Paresthesia of the hands and feet had diminished, and the patient was able to write with greater facility, to tie his necktie and button his clothes better than previously. Objectively there was decided improvement.

Another neurologic examination was carried out on July 10. The pupils remained rather small and somewhat irregular; reaction to light was somewhat impaired. The achilles tendon reflexes were still relatively active. The Babinski and Chaddock reflexes were still slightly pathologic. Appreciation of vibratory sensibility was normal over the iliac crests and only slightly impaired over the malleoli. The tingling had practically disappeared from the fingers and toes and was present only at times in the fingers of the right hand, particularly, and in the second and third digits of the left hand. The patient no longer complained of stiffness and awkwardness of the extremities. There was great improvement in his general strength, and he had no difficulty in walking, even in the dark. Subjectively and objectively there had been great improvement.

Reexamination on April 22, 1936, revealed that the right pupil was somewhat larger than the left; both pupils reacted normally to light and in convergence. The tendon reflexes were still more active than normal. The Babinski reflex was now normal. Vibratory and joint sensibility were normal, as was stereognosis. The general health of the patient was only fair. Some diarrhea was present, but there had been no glossitis. Because of economic conditions he had not received intramuscular injections of liver extract for five months. It is likely that the omission of liver extract had been responsible in part for the return of some symptoms.

The important neurologic findings which may occasionally be observed with sprue, nontropical sprue and idiopathic steatorrhea and which are dependent on organic involvement of the nervous system usually express themselves as persistent acroparesthesias, depression of the tendon reflexes, especially those of the lower extremities, impairment of vibratory sensibility, as observed over the iliac crests and malleoli, and impairment of postural sensibility in the toes. One case has been reported in which the clinical findings indicated subacute com-

bined degeneration of the spinal cord and, if persistent paresthesias may be so interpreted, degeneration of the peripheral nerves (although the tendon reflexes were not impaired). These clinical findings disappeared after intensive intramuscular administration of liver extract.

SUMMARY

Subacute combined degeneration of the spinal cord has come to involve a major problem that revolves around the type seen typically with pernicious anemia. More than sixty associated conditions or causes have been advanced for combined degeneration that often is said to be "just like that of pernicious anemia." The legitimate and important question has been raised before as to the accuracy and implications of some of these observations and whether the typical clinical and pathologic picture does not carry with it an import that in some manner attaches specifically to a factor unknown but commonly associated with pernicious anemia.

The funiculi of the spinal cord may be altered by many diseases and in many ways. The differential diagnosis cannot always be made on clinical evidence alone. Before a cause of subacute combined degeneration of the spinal cord like that which occurs in cases of pernicious anemia can rightly be assigned, typical and well developed clinical and pathologic observations must be brought forward as evidence. On the basis of a survey of the important available literature, it appears that this familiar and challenging picture may be brought about by chronic alcoholism, gastric carcinoma, obstruction and fistulas of the intestinal tract, pernicious anemia, so-called prepernicious anemia and scurvy (this may have been a complication). It possibly may be similarly related to pancreatitis, pellagra and hemolytic icterus, and it has been in some manner associated with amyotrophic lateral sclerosis and a number of unclassified diseases.

An important physiologic principle appears to be involved. Careful hematologic studies, gastric analysis and an investigation of the presence of Castle's intrinsic factor, if facilities are available, possibly would lead to the disclosure of some one underlying cause, probably nutritional and in the nature of a deficiency.

We have studied 77 cases in which there were signs of involvement of the posterior and of the lateral columns of the spinal cord and in which free hydrochloric acid was present in the gastric contents. The latter finding practically eliminates pernicious anemia as a cause of the involvement. When gradually developing, symmetrical, persistent paresthesias of the hands and feet are added, the clinical neurologic picture becomes that seen typically in cases of pernicious anemia. There were 8 cases in which these symptoms were present; in 3 of these there

was no reason for believing that a nutritional factor entered into the cause; in the remaining 5 there was reason for thinking so, although we do not venture to say that the pathologic examination in these cases would have disclosed classic subacute combined degeneration of the spinal cord. To borrow a term from the serologic laboratory, occasional "false positive" results, which are indistinguishable clinically at a given time from the picture typically seen with pernicious anemia, may be observed. In cases in which the diagnosis is doubtful an examination of the spinal fluid increases the accuracy of the diagnosis. In none of these cases could the exact pathologic nature of the lesion in the cord be verified.

In a review of more than two hundred available articles on the subject of sprue it was found that only twenty included evidence of organic involvement of the nervous system.

Gastric analysis revealed the presence of free hydrochloric acid in 52 of the 93 cases of sprue and related conditions which have been observed at the clinic. The presence of free hydrochloric acid was regarded as presumptive evidence that no cases of pernicious anemia were included in this study. Neurologic examination was performed in 29 of the 52 cases.

In 11 of these 29 cases there was evidence of organic involvement of the nervous system. In 6 of these cases there had been continuous paresthesias of the hands and feet; in 6 cases the tendon reflexes were diminished or absent, and in 1 case they were increased; in 10 cases vibratory sensibility was impaired or absent, usually at both iliac crests and at the malleoli. Macrocytosis was present in 8 cases. One case has been reported in which the clinical findings indicated subacute combined degeneration of the spinal cord. These clinical findings disappeared after intensive intramuscular administration of liver extract.

ELECTROLYTE BALANCE DURING RECOVERY FROM MERCURY BICHLORIDE POISONING

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In the body fluids of patients suffering from acute mercury poisoning the changes in the concentration of electrolytes may be profound. Few other diseases are associated with a greater disturbance of acid-base equilibrium than is observed in this condition. Addison's disease,[1] diabetic coma [2] and heat cramps [3] are examples of morbid conditions which are associated with recovery as the disordered equilibrium is corrected. Advanced renal insufficiency, on the other hand, is a disease with electrolyte imbalance which resists restoration to normal and ends with a disintegration of the chemical structure of the body.[4] Acute mercury poisoning sometimes belongs in one category, sometimes in the other. In this communication there will be described the several changes in the concentration of electrolytes in a patient who recovered from acute and severe mercury poisoning.

The amount of mercury bichloride which was ingested was believed to have been 1 Gm. Usually this amount is not fatal;[5] nevertheless, it

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From the Medical Clinic of the Massachusetts General Hospital and the Fatigue Laboratory, Harvard University.

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was followed in this case by hematemesis, melena, anuria, uremia and coma. Convalescence was satisfactory but was sufficiently slow to permit us to use and to evaluate several therapeutic procedures. Our principal interest in this communication is the presentation of data obtained during the correction of the disordered equilibrium. In addition there will be discussed other data which aid in the explanation of the secretion of urine by the various physiologic units in the kidney of vertebrates.

REPORT OF CASE

Mrs. L. N., a 32 year old housewife, was admitted to the Massachusetts General Hospital on March 16, 1935, having suffered from anuria for six days and from coma for thirty-six hours. Seven days before admission to the hospital she ingested about 1 Gm. of mercury bichloride during a temporary state of depression related to a postpuerperal psychosis. Shortly after the ingestion of the mercury salt, violent emesis began. The patient collapsed, and she was found unconscious on the bathroom floor by her relatives. The time between ingestion and emesis was estimated from five to fifteen minutes. After regaining consciousness the patient was taken to a local hospital and observed for seven days. During the first eighteen hours small amounts of dark, smoky urine were voided. Suppression followed, and during the ensuing six days less than 100 cc. of bloody urine was voided spontaneously or was obtained by catheter. During this time the patient vomited frequently each day, had unremitting bloody diarrhea and, in consequence, probably assimilated little or none of the food ingested. An infusion of 1,000 cc. of saline solution was given on March 12 and 14 and a transfusion of 500 cc. of whole blood on March 15.

The patient's past history was unimportant.

On admission to the Massachusetts General Hospital the patient was in a comatose state. The respiratory rate was rapid, and she perspired profusely and regurgitated small amounts of bile-colored fluid. There was dermatitis on the face. The pupils were contracted and did not react to light. The examination of the fundi revealed no abnormality. The auscultatory findings for the heart and lungs were normal. The heart rate at the apex was 100 per minute and regular. The blood pressure, which was 150 systolic and 100 diastolic when the patient entered the hospital, decreased after a few hours to 130 systolic and 80 diastolic and remained at this level during her stay in the hospital. Examination of the abdomen revealed slight epigastric tenderness. The rectal temperature was 37.8 C. (100 F.).

The results of the laboratory studies were as follows: The red blood cell count was 4,130,000. The white blood cell count was 17,800, with 80 per cent polymorphonuclears. The blood cells in the stained smear appeared to be normal. The hemoglobin value was 80 per cent (Tallqvist). The Hinton reaction of the blood was negative. The specific gravity of the urine was 1.008. There was a slight trace of albumin in the urine, as shown by the heat test. The urinary sediment contained many red and white blood cells. The tests for the presence of sugar and ketone bodies gave negative results. The first stools passed after the patient's admission to the hospital definitely showed the presence of blood.

A roentgenographic study of the esophagus, stomach and small intestines three weeks after the ingestion of the poison revealed no abnormality.

After the patient's admission to the hospital large amounts of sodium chloride were given parenterally, according to the method of Peters and his associates.[5a] During the first thirty hours a total of 100 cc. of bloody urine was obtained by catheterization. On March 18 the patient voided spontaneously 450 cc. of cloudy urine. During the remainder of her stay at the hospital the daily volume of urine was greater than 1,000 cc. The volume of vomitus varied from 90 to 1,400 cc. per day. On March 21 80 milliequivalents of racemic sodium lactate was given intravenously. A similar amount was given on two of the three following days. From March 25 to 29 calcium lactate was given by mouth in amounts varying from 4.2 to 12.6 milliequivalents. On March 29 a transfusion of 500 cc. of whole blood was given.

The mental condition of the patient improved during her stay in the hospital. She was discharged on April 2 and returned to her home. Two follow-up visits to the hospital were made. The last visit took place five months after the ingestion of the mercury bichloride. Except for a diminished concentration of hemoglobin, a slightly increased concentration of nonprotein nitrogen and a low urinary specific gravity, the results of studies at that time were normal.

Methods.—The determinations on the blood were made with specimens of arterial blood which were collected anaerobically. Except for the specimens taken on March 16 and the second sample on March 21, all were obtained while the patient was fasting and at least eight hours after the last parenteral injection of the previous day. Specimens of urine were collected in twenty-four hour amounts, preserved under toluene and stored at a temperature below 4 C. The calculation of the p_H of arterial serum has been described.[6] On certain days observations were not made on equilibrated blood. On these days the value for the carbon dioxide tension was derived from the data of Henderson,[7] and the p_H was calculated. The error in calculating p_H in this fashion is not significant. The methods employed for analysis of blood and urine have been reported elsewhere.[8] This patient was not studied in the research ward, but she was under the constant supervision of graduate nurses, and the data regarding fluid and salt exchange are thought to be reliable.

Blood.—The data for the constituents of the plasma and whole blood are given in table 1. Severe acidosis was observed in the first specimen of blood, and as late as the morning of March 21, twelve days after the onset of the illness, the p_H had not exceeded 7.21. The acidosis was associated with a diminished alkali reserve, a diminished concentration of fixed base and an increased concentration of undetermined acid. An unfavorable prognosis was given this patient

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TABLE 1.—*Experimental Observations on Arterial Blood*

Date, 1935	Whole Blood					True Plasma											
	Day of Illness	Total Carbon Dioxide, M. Eq. per Liter	Carbon Dioxide Tension, Mm. of Hg	Oxygen Capacity, M. Eq. per Liter	Cell Volume, Cc. per 100 Cc.	p_H	Total Fixed Base, M. Eq. per Liter	Sodium, M. Eq. per Liter	Calcium, M. Eq. per Liter	Bicarbonate, M. Eq. per Liter	Chloride, M. Eq. per Liter	Phosphate, M. Eq. per Liter	Proteinate, M. Eq. per Liter	Urate, M. Eq. per Liter	Undetermined Acid, M. Eq. per Liter	Sugar, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.
March 16†	7	9.1	27.2*	6.92	34.9	7.19*	134.1	125.0	3.3	9.6	82.2	4.2	10.5	0.73	26.7	94	260
18	9	9.1	27.0	6.76	30.5	7.18	140.4	134.8	...	9.4	88.8	...	9.7	0.77	....	101	260
19	10	...	25.0*	....	32.6	7.20*	141.6	129.5	3.3	9.0	96.4	3.0	10.0	0.83	25.4	91	235
20	11	8.4	24.6	6.41	30.4	7.18	148.3	136.4	...	8.5	100.8	...	12.1	0.74	....	97	180
21	12	8.8	25.5*	....	29.8	7.21*	145.1	141.7	3.1	9.2	104.6	2.1	11.3	....	....	85	190
21†	12	11.2	26.7*	....	26.4	7.30*	143.4	134.3	...	12.0	105.7	...	....	....	....	..	...
22	13	11.3	26.9*	....	27.6	7.29*	142.2	134.3	...	11.7	104.2	...	11.9	0.58	....	..	160
23	14	14.1	28.5	5.77	25.8	7.35	147.2	136.2	3.0	14.5	104.2	2.0	11.2	0.54	14.8	..	140
25	16	21.8	34.2	4.90	23.9	7.48	143.9	133.2	...	23.2	99.0	...	13.4	....	....	..	120
27	18	28.8	40.9	5.05	24.4	7.52	149.8	135.1	3.7	31.0	94.0	1.0	16.4	0.26	7.2	..	90
30	21	22.6	40.0	6.04	33.4	7.43	153.0	141.9	4.7	24.5	104.2	0.8	16.8	0.20	6.5	..	55
April 2	24	21.7	39.8	5.85	30.2	7.42	150.7	138.3	...	24.0	103.8	...	18.8	0.18	...	..	35
30	52	20.9	42.0	6.94	35.2	7.39	147.0	136.7	...	23.3	102.8	...	16.9	0.30	...	..	39
Aug. 19	163	....	....	7.73	38.8	....	149.5	137.3	5.3	21.7	104.8	1.1	16.9	....	...	..	..

* Calculated indirectly.

† Blood drawn at 9 p. m.

because of the duration and severity of the acidosis. In a series of thirty-seven patients suffering from mercury poisoning, Peters and his associates [5a] observed no recovery among those for whom the bicarbonate concentration was below 10 milliequivalents per liter. When this patient was admitted the bicarbonate concentration was 9.6 milliequivalents per liter, and it remained below 10 milliequivalents until March 21. The concentration of undetermined acid in the first specimen of blood was about 27 milliequivalents per liter. The acids which they replaced were principally bicarbonate and chloride. The exact nature of these undetermined acids is not known. Ketone bodies were not present in these specimens of urine, and it is assumed, therefore, that there was no ketonemia. The concentrations of lactate and sulfate were not determined.

The maximal depletion of plasma chloride was approximately 20 milliequivalents per liter; that of plasma sodium, approximately 15 milliequivalents per liter. These were observed in the first specimen of blood. The diminished concentration of these constituents was probably associated with a similar decrease in their concentration in the interstitial fluids.[3] If this assumption is correct, the negative balance was great during the first week of illness. At least four processes were responsible for the depletion: 1. The diuresis which followed the ingestion of the mercury salt was probably accompanied with an increased excretion of sodium and chloride.[9] 2. The excretion of gastro-intestinal juices during the excessive vomiting and diarrhea caused a further drain on the electrolytes of the body fluid.[10] 3. The loss of electrolytes from sweating was probably great during the first days of illness. 4. There was an inadequate ingestion of the food and mineral salts which are normally consumed.

The treatment with saline solution parenterally during the first five days was accompanied with a return to normal of the concentrations of plasma sodium and chloride. On the morning of March 21 the sodium concentration was 141.7 milliequivalents per liter, and the chloride concentration was 104.6 per liter. In contrast to these changes was the consistently low concentration of bicarbonate. In spite of the administration of large amounts of base as sodium chloride, the alkali reserve did not increase until the evening of March 21. On this day 80 milliequivalents of racemic sodium lactate [11] was given intravenously. Twenty-four hours later the bicarbonate concentration had increased 2.8 milliequivalents per liter, and the p_H had increased from 7.21 to 7.30. The injections of racemic sodium lactate were continued until March 25. On this day the p_H was 7.48, and the bicarbonate concentration was 23.2 milliequivalents per liter.

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9. MacNider, W. de B.: On the Elimination of Phenolsulphonephthalein in Acute Mercuric Chlorid Intoxication, Proc. Soc. Exper. Biol. & Med. **18**:73, 1920. Fulton, M. N.; Van Auken, H. A.; Parsons, R. J., and Davenport, L. F.: The Comparative Effect of Various Diuretics in Dogs, with Special Reference to the Excretion of Urine, Chloride, and Urea, J. Pharmacol. & Exper. Therap. **50**:223, 1934.

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From March 21 to 28 the increase in concentration of plasma bicarbonate was approximately 22 milliequivalents per liter. Simultaneous with this increase there was a decrease of 10 milliequivalents per liter in concentration of plasma chloride. The familiar reciprocal relationship between concentration of bicarbonate and concentration of chloride is shown in the chart that accompanies this article. During this period the concentration of total base increased 5 milliequivalents per liter, and the concentration of undetermined acid decreased about 19 milliequivalents per liter. Thus the sum of the increase of bicarbonate and base (27 milliequivalents) is approximately equal to the sum of the decrease of chloride and undetermined acid (29 milliequivalents).

The decrease in concentration of total fixed base at the time of the patient's entry into the hospital was principally a depletion of the sodium fraction but not exclusively. The concentration of calcium in the first specimen of blood was 3.3 milliequivalents per liter. The concentration of ionized calcium in the same sample, calculated according to the method of McLean and Hastings,[12] was 1.9 milliequivalents per kilogram of water. This is below the average given by them for normal subjects. The ingestion of calcium lactate was begun on March 25. The return of the concentration of total calcium and ionized calcium toward normal was associated with the daily ingestion of this salt and a transfusion of whole blood on March 29. Four months after the patient's discharge from the hospital the concentration of serum calcium was 5.3 milliequivalents per liter.

The concentration of serum phosphate when the patient was admitted was 4.2 milliequivalents per liter, approximately five times normal. This increase was a function of at least two processes: 1. In certain disturbances of acid-base equilibrium an increased concentration of serum phosphate follows a diminution in concentration of serum calcium. 2. A characteristic sequela of renal insufficiency is an increase in the phosphate value.[4] The concentration of this constituent decreased steadily during the patient's stay in the hospital, and on March 30 it was 0.8 milliequivalents per liter.

Associated with the increased concentration of serum phosphate was the increased concentration of nitrogenous products. On March 16 the concentration of nonprotein nitrogen was 260 mg. per hundred cubic centimeters, and the urate value was 0.72 milliequivalents per liter. After the parenteral administration of large amounts of sodium chloride and water, the urinary flow was reestablished, and the concentration of nonprotein nitrogen decreased. The concentration of urate, however, remained at a high level for several days and began to decrease only after the concentrations of sodium and chloride in the plasma were normal. This may be interpreted as evidence that the kidney contributes to the metabolism of uric acid in the body, in addition to its function as the principal excretory organ for this substance.

The loss of protein and hemoglobin from the circulating blood probably was as large as 30 per cent. The concentration of plasma proteinate at the time of the patient's admission to the hospital was 10.5 milliequivalents per liter (4.9 Gm. per hundred cubic centimeters expressed as plasma protein), and the oxygen capacity was 6.9 milliequivalents per liter. The concentration of plasma proteinate increased as the dietary intake of the patient approached normal. The concentration of hemoglobin in the blood, however, continued to decrease. On March 27

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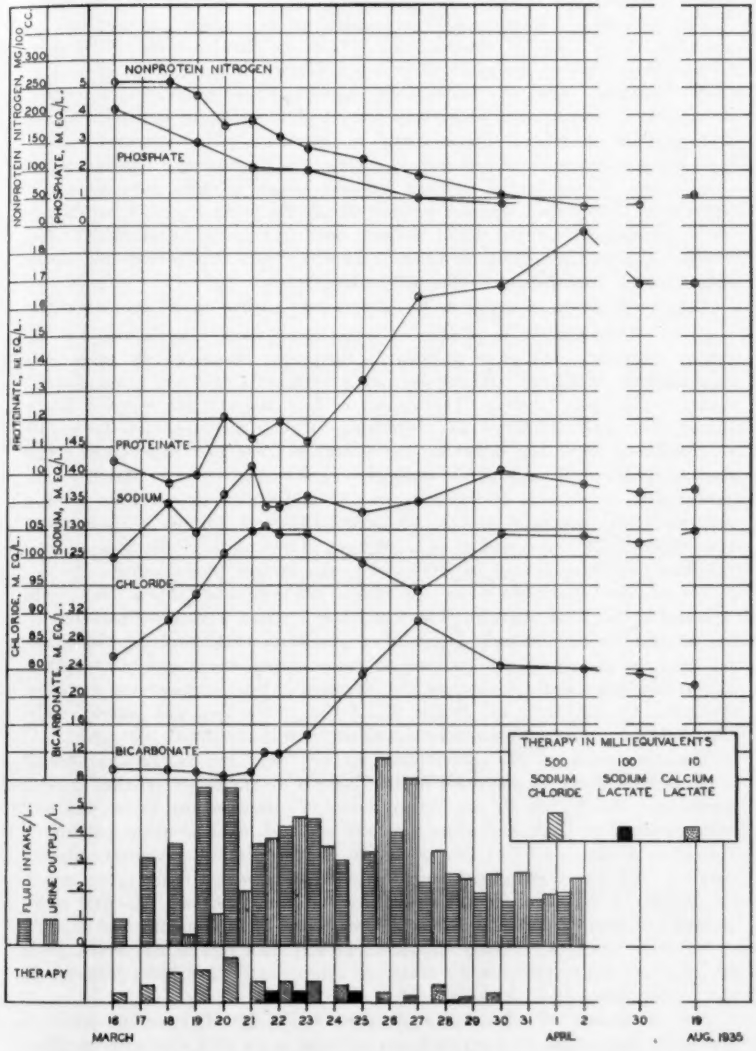

Experimental data on the intake and output of fluid, the concentration of certain constituents of the blood and therapy. The urine excreted on March 24 was discarded.

the oxygen capacity was 1.8 milliequivalents per liter less than at the time of the patient's entry into the hospital, and five months after the onset of the illness it was still below the average value for women.

The diminished concentration of proteinate and hemoglobin on entry can be accounted for by a loss of these substances from the circulating blood.[5a] During the first three days of treatment there was a further decrease in the content of plasma proteinate. After this transient decrease, which was produced by hydration, the proteinate concentration returned to normal. The failure of the concentration of hemoglobin to return simultaneously is interesting. The continued loss of blood did not appear to be sufficient to explain this discrepancy. Damage to the hematopoietic system by the mercury bichloride seems to be a more acceptable explanation. The patient was not weighed during the acute stages of her illness, and determinations of the blood volume were not made. Quantitative data concerning dehydration must be deduced, therefore, from the protein and hemoglobin values. This method is obviously unsatisfactory.

The concentration of sugar in the plasma was normal in all determinations.

Urine.—The data for the intake of water and sodium chloride and for the urinary constituents are given in table 2. Electrolyte studies of the urine were not made until March 19. On this day nearly 6 liters of fluid was given, and the urinary volume was 1,190 cc. The amount of base and chloride excreted as the urinary flow was established was surprising. It was assumed that the tissues were suffering from salt depletion, and it was believed that they would retain most of the available salt. This sequence was not observed. On March 19 the concentration of chloride in the urine was 87 milliequivalents per liter, about 6 milliequivalents less than the concentration of plasma chloride. Similar data were obtained for concentration of fixed base. The failure of the body to keep back base and chloride may be attributed to the damage to the kidneys.

The principal electrolyte in the total base of the urine was sodium. This can be explained by the large amounts of sodium chloride which were given parenterally. The absence of an increased excretion of potassium (calculated by difference) indicates that an excessive breakdown of tissue during anuria had not occurred. This is consistent with the data for the excretion of total nitrogen and inorganic phosphate. On March 19 and 20 less than 6 Gm. of nitrogen was excreted daily. The intake of protein on these days accounted for this amount of nitrogen.

The comparison of the concentration of uric acid and inorganic phosphate in the urine with the concentration in the blood is of interest in relation to renal physiology. On March 19 the concentration of urate in the urine was 0.68 milliequivalents per liter, and in the serum it was 0.96 milliequivalents per liter.[13] This gives a ratio of 0.7 if the calculation is based on water content. On the same day the ratio of inorganic phosphate in the urine to that in the serum was 1. On March 23 the ratio for urate was 2.4 and for phosphate 1.5. The ratios continued to increase during recovery, and on March 30 the concentration of urate in the urine was approximately nine times greater than that in the serum, while the phosphate concentration in the urine was approximately five times greater than that in the serum.

Six milligrams of phenolsulfonphthalein was injected intramuscularly on March 24. Approximately 2 per cent was excreted in the first hour after injection and the same amount in the second hour. One week later a similar amount of

13. In this discussion of electrolyte ratios it is assumed that all the urate is present as acid and not bound by base.

TABLE 2.—*Daily Observations on Intake and Urinary Output*

Date, 1936	Intake: Parenteral, Fluid, Cc.	Intake: Oral Fluid, Cc.	Intake: Sodium Chloride (Parenteral), M. Eq.	Urinary Constituents: Volume, Cc.	Specific Gravity	Sodium, M. Eq.	Calcium, M. Eq.	Total Fixed Base, M. Eq.	Chloride, M. Eq.	Inorganic Phosphate, Mg.	Total Nitrogen, Gm.	Ammonia, M. Eq.	Urea Nitrogen, Gm.	Uric Acid, Mg.	Albumin	White Blood Cells	Red Blood Cells	Casts	Sugar	Therapy
March 16*	1,000	0	154	0	.....	...	...	...	...	...	.....	...	....	...	++	++++	++++	0	..	
17	2,000	1,200	308	100	.....	...	...	...	...	...	.....	...	....	...	++	++++	++++	+	..	
18	3,500	200	540	450	.....	...	...	...	...	...	.....	...	....	...	+	++++	++++	0	..	
19	3,800	1,900	588	1,190	1.008	98	1.5	118	103	151	3.94	54	2.11	137	++++	++++	++	+	+	
20	5,300	400	818	2,000	1.010	178	2.1	199	184	252	5.78	67	2.43	281	+	++	+	0	+	
21	2,600	1,100	385	3,900	1.008	365	4.0	404	364	634	10.80	...	....	832	.....	.....	.....	..	0	Racemic sodium lactate, 80 m. eq., intravenous
22	2,600	1,700	385	4,670	1.004	422	4.4	466	427	632	12.52	166	7.56	899	.....	.....	.....	..	0	Racemic sodium lactate, 80 m. eq., intravenous
23	2,600	2,000	385	3,600	1.002	308	3.3	343	305	425	9.43	75	6.41	768	.....	.....	.....	..	+	
24	2,000	1,100	308	.....	.....	...	...	...	...	...	.....	...	....	...	.....	.....	.....	..	+	Racemic sodium lactate, 80 m. eq., intravenous
25	600	2,800	0	6,800	1.004	567	7.4	614	543	588	16.05	...	....	1,630	.....	.....	.....	..	+	Calcium lactate, 7.48 m. eq., by mouth
26	0	4,100	0	6,050	1.004	514	7.4	566	465	423	14.57	...	....	945	+	+	+	0	0	Calcium lactate, 5.85 m. eq., by mouth
27	0	2,300	0	3,480	1.002	308	5.1	356	252	224	11.06	...	....	770	.....	.....	.....	..	0	Calcium lactate, 12.66 m. eq., by mouth
28	600	2,000	45	2,450	1.004	244	4.4	269	195	177	8.16	...	....	580	.....	.....	.....	..	0	Calcium lactate, 4.22 m. eq., by mouth
29	0	1,900	0	2,640	1.006	278	5.5	312	240	256	9.48	...	....	874	.....	.....	.....	..	..	Calcium lactate, 6.52 m. eq., by mouth; transfusion of whole blood, 500 cc.
30	0	1,600	0	2,660	1.002	284	5.8	338	263	380	10.62	142	6.44	854	.....	.....	.....	..	..	
31	0	1,700	0	1,900	1.004	163	6.8	211	165	437	9.60	104	6.11	756	.....	.....	.....	..	..	
April 1	0	1,950	0	2,480	1.004	215	7.6	279	205	640	11.44	113	7.80	1,085	0	.....	.....	..	..	
30	..	.....	..	.....	1.002	...	...	...	...	...	.....	...	....	...	0	0	0	0	..	
Aug. 19	..	.....	..	.....	.....	...	...	...	...	...	.....	...	....	...	0	0	0	0	..	

* Four hours.

dye was injected intravenously, and 20 per cent was excreted in the first fifteen minutes. At the end of two hours 48 per cent was excreted. In two subsequent tests, given on April 30 and August 19, 25 and 40 per cent, respectively, were excreted during the first fifteen minutes.

Albumin, blood cells and casts are observed frequently in the urine of patients suffering from mercury poisoning.[14] The disappearance of these substances in this case required but a few days. The specific gravity of the urine did not exceed 1.010 during the patient's stay in the hospital or at the follow-up visits.

INDUCTIONS CONCERNING THE VERTEBRATE KIDNEY

The site of the damage to the renal architecture in acute experimental mercury poisoning is principally in the tubules.[15] The glomeruli suffer less. The chemical findings which are presented in this communication are in agreement with these data. During the first days of treatment the respective concentrations of chloride, phosphate and urate in serum and urine were similar. At the time when the kidneys resumed the secretion of urine, the fluid passed was essentially a plasma filtrate, and the contribution to renal function by the tubules was minimal. This supposition is consistent with the data of Richards and his associates [16] concerning the nature of the glomerular filtrate of the amphibian kidney. The urine was not exclusively a plasma filtrate, however, for dextrose was absent [17] from the specimens obtained on March 17 and 18. This phenomenon may be accounted for in at least two ways. Either selective damage was done to the functioning area of the tubules or different segments of the tubules have different functions. The latter explanation

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16. Bordley, J., and Richards, A. N.: Quantitative Studies of the Composition of Glomerular Urine: VIII. The Concentration of Uric Acid in Glomerular Urine of Snakes and Frogs, Determined by an Ultramicroadaptation of Folin's Method, J. Biol. Chem. **101**:193, 1933. Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine: X. The Concentration of Inorganic Phosphate in Glomerular Urine from Frogs and Necturi Determined by an Ultramicromodification of the Bell-Doisy Method, ibid. **101**:239, 1933. Westfall, B. B.; Findley, T., and Richards, A. N.: Quantitative Studies of the Composition of Glomerular Urine: XII. The Concentration of Chlorids in Glomerular Urine of Frogs and Necturi, ibid. **107**:661, 1934.

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is consistent with the observations of Menten [18] and Richards [19] that only certain parts of the tubules are damaged by mercury poisoning. After the first days of relative tubular inactivity it is assumed that there was a rapid return of their function. This assumption is based on the increase in concentration of chloride, urate and phosphate in the urine. The data on the excretion of phenolsulfonphthalein dye further substantiates this hypothesis. Marshall [20] has shown that in uninjured kidneys this dye is excreted by the tubules. On March 24 only minimal amounts of the dye were excreted, while seven days later 48 per cent of the total amount injected was excreted.

SUMMARY

Studies of the blood and urine of a patient suffering from acute mercury poisoning are reported. After the ingestion of a sublethal dose of mercury bichloride there was a six day period of anuria. The observations reported began on the seventh day and continued through convalescence. Five months after the onset the patient had resumed her household duties, and in most instances the results of examination of the blood and urine appeared to be normal.

The changes in concentration of electrolytes and nonelectrolytes in the body fluids were (1) depletion of base and chloride, (2) an increased concentration of undetermined acid, (3) retention of phosphate and nitrogenous products and (4) loss of serum protein and hemoglobin. The treatment was devised to restore to normal the disordered acid-base equilibrium. The administration of large amounts of saline solution during anuria was thought to have been beneficial rather than injurious. The data presented are consistent with the interpretation that in acute mercury poisoning the principal renal damage is in the tubules.

18. Menten, M. L.: Pathological Lesions Produced in the Kidney by Small Doses of Mercuric Chloride, J. M. Research **43**:315, 1922.

19. Richards, A. N.: Direct Observations of Changes in Function of the Renal Tubules Caused by Certain Poisons, Tr. A. Am. Physicians **44**:64, 1929.

20. Marshall, E. K., Jr.: The Secretion of Phenol Red by the Mammalian Kidney, Am. J. Physiol. **99**:77, 1931.

MECHANISM OF EXPERIMENTAL UREMIA

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In a previous communication [1] it was shown that changes in the electrolyte pattern of the cerebrospinal fluid of dogs produced by intracisternal injections caused muscular twitching, a rise in blood pressure and disturbances of breathing. The similarity of this syndrome to that exhibited by certain patients with renal insufficiency has led to a study of experimental uremia. In the present communication no attempt will be made to summarize the extensive literature on the subject. Discussions of previous work are to be found in the publications of Fishberg,[2] Becher [3] and Harrison and Mason.[4]

EXPERIMENTAL METHODS

Dogs were used as experimental subjects. Measurements of the blood pressure were made by a modification of the technic of Ferris and Hynes,[5] the cuff employed being similar to theirs but the passage of the pulse wave being determined by palpation of the dorsal artery of the hindfoot rather than by auscultation. The results obtained by this method were found to compare satisfactorily with the

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1. Resnik, H., Jr.; Mason, M. F.; Terry, R. T.; Pilcher, C., and Harrison, T. R.: The Effect of Injecting Certain Electrolytes into the Cisterna Magna on the Blood Pressure, Am. J. M. Sc. **191**:835, 1936.

2. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

3. Becher, E.: Pathogenese, Symptomatologie und Therapie der Urämie, Ergebn. d. ges. Med. **18**:51, 1933.

4. Harrison, T. R., and Mason, M. F.: Pathogenesis of the Uremic Syndrome, Medicine **16**:1, 1937.

5. Ferris, H. W., and Hynes, J. F.: Indirect Blood Pressure Readings in Dogs: Description of Method and Report of Results, J. Lab. & Clin. Med. **16**:597, 1931.

graphic records of mean blood pressure obtained by connecting a mercury manometer to the cannulated femoral artery of the opposite leg. The effect of epinephrine on the values obtained by the two methods is illustrated in chart 1.

After repeated measurements of the blood pressure for several days had been made as controls, uremia was produced by bilateral nephrectomy, bilateral ureteral ligation or ligation of the renal arteries. After the operation the animals were observed once or twice daily, the blood pressure being taken and symptoms recorded. Samples of blood and cerebrospinal fluid were obtained at various times both preoperatively and postoperatively for chemical analysis.

In addition to these observations on uremic animals, attempts were made to investigate the toxicity of some of the substances retained in the body of uremic dogs by injecting the compounds into normal animals.

The analytic determinations were made as follows: nonprotein nitrogen according to the method of Folin and Wu,[6] plasma chloride according to Whitehorn's[7] method, total serum calcium according to the Clark and Collip[8] modification of the Kramer-Tisdall technic, inorganic phosphate according to Bodansky's[9] modi-

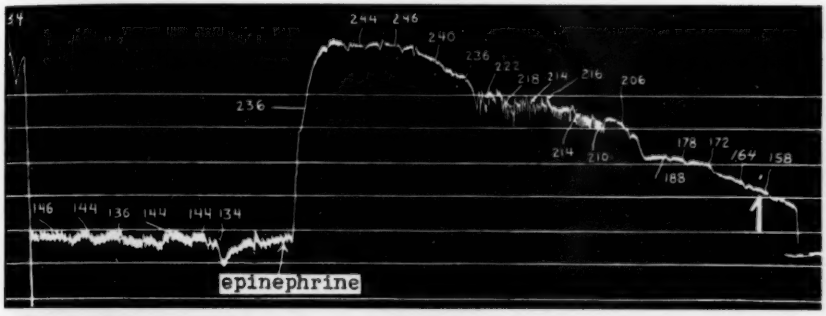

Chart 1.—The curve passes from left to right. The distance between the adjacent horizontal lines indicates 20 mm. of mercury. The femoral artery was cannulated on one side. Repeated measurements of blood pressure were made on the other leg by the cuff method mentioned in the text. The numbers on the record signify the readings obtained. As can be seen, the results of the two methods were in substantial agreement. Since the mercury manometer records the mean pressure rather than the actual systolic pressure, it is evident that the values obtained with the cuff method are somewhat below the systolic pressure and represent an approximation of the mean arterial pressure.

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6. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

7. Whitehorn, J. C.: A Simplified Method for the Determination of Chlorides in Blood or Plasma, J. Biol. Chem. **45**:449, 1921.

8. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

9. Bodansky, A.: Determination of Inorganic Phosphate, Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**: 197, 1932.

fication of the Kuttner-Cohen [10] method, carbon dioxide content with the Van Slyke-Neill [11] manometric apparatus, p_H of plasma and cerebrospinal fluid by the Hastings-Sendroy [12] bicolorimetric procedure, ionized calcium of serum and cerebrospinal fluid by the frog-heart method of McLean and Hastings,[13] blood phenols by the Rakestraw [14] adaptation of the method of Folin and Denis [15] and guanidine according to the directions of Minot and Dodd.[16] It should be noted that the latter two methods are not highly specific. By the former method certain related compounds as well as phenols are measured; likewise, by the latter method substances probably related to guanidine are measured along with guanidine itself.

A. THE CLINICAL PICTURE OF EXPERIMENTAL ANURIA IN DOGS

The clinical symptoms were similar to those described by Herter [17] and are summarized in table 1. During the first twenty-four hours the animals usually appeared to be normal except for slight weakness, which could be ascribed to the operative procedure. Gastro-intestinal disturbances, characterized by vomiting and occasionally by diarrhea, usually appeared about forty-eight hours after the operation. Changes in blood pressure were observed in most of the animals. After ureteral ligation the blood pressure tended to be elevated. Inconstant changes were observed after bilateral nephrectomy, some of the animals displaying a definite elevation on the second and third postoperative days, followed by hypotension in almost all the animals on the fourth day. The reasons for differences in behavior of the animals as regards blood pressure will be discussed later.

The most striking changes had to do with the nervous system. On the second and third postoperative days many of the animals exhibited an increase in muscular irritability which subsequently disappeared.

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10. Kuttner, T., and Cohen, H. R.: The Micro-Estimation of Phosphorus and Calicium in Pus, Plasma and Spinal Fluid, J. Biol. Chem. **75**:517, 1927.

11. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

12. Hastings, A. B., and Sendroy, J., Jr.: The Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**: 695, 1924.

13. McLean, F. C., and Hastings, A. B.: Biological Method for Estimation of Calcium Ion Concentration, J. Biol. Chem. **107**:337, 1934.

14. Rakestraw, N. W.: A Quantitative Method for the Determination of Phenols in Blood, J. Biol. Chem. **56**:109, 1923.

15. Folin, O., and Denis, W.: A Colorimetric Method for the Determination of Phenols (and Phenol Derivatives) in Urine, J. Biol. Chem. **22**:305, 1915.

16. Minot, A. S., and Dodd, K.: Guanidine Intoxication: A Complicating Factor in Certain Clinical Conditions of Children, Am. J. Dis. Child. **46**:522 (Sept.) 1933.

17. Herter, C. A.: The Results of Experimental Nephrectomy in Dogs as Bearing upon the Uraemic State, M. Rec. **52**:280, 1897.

Apathy and weakness beginning on the second day were progressive, and stupor frequently occurred by the fourth day; however, true coma was rarely observed. Convulsions were occasionally encountered in these later stages.

The anuric animals, of course, displayed a steady rise in the nonprotein nitrogen content of the blood. There was a less marked diminution in the chloride content of the plasma (chart 2).

Two distinct impressions were gained by the observation of anuric dogs: First, the general condition was similar to that of patients with renal insufficiency, and second, each animal behaved as if its nervous system were being subjected to two antagonistic influences, one tending to stimulate it and the other to depress it. In some animals the former

TABLE 1.—*Symptoms Observed in Dogs with Experimental Anuria* *

				Disturbances of Nervous System							
				Manifestations of Depression		Manifestations of Stimulation			Gastro-Intestinal Disturbances		
Operative Procedure	Days After Operation	Number of Animals Observed	Average Changes in Blood Pressure, Mm. Hg	Weakness or Apathy	Stupor or Coma	Twitching	Convulsions	Excitement	Vomiting	Diarrhea	Respiratory Disturbances
Bilateral nephrectomy	1	8	— 4	+	0	+	0	0	0	0	+
	2	7	— 2	+++	0	++	0	+	+	0	+
	3	8	+ 1	+++	0	++	0	+	+++	0	0
	4	7	—28	++++	++	+++	++	0	+++	++	0
Ligation of both ureters	1	14	+ 2	++	+	0	0	0	+	0	0
	2	11	+16	++	0	+	0	+	+++	0	+
	3	13	+33	+++	+	++	+	0	++	0	+
	4	5	+19	++++	0	++	0	0	++	+	0

* + indicates observed in 25 per cent or less of the animals; ++, observed in 26 to 50 per cent of the animals; +++, observed in 51 to 75 per cent of the animals, and ++++, observed in more than 75 per cent of the animals.

influence had the ascendency; in some the latter was more outspoken. More frequently an animal would successively display symptoms of stimulation and then of depression; and not uncommonly, although paradoxically, the same animal at a given time would exhibit signs of both depression and stimulation of the nervous system. An adequate explanation of the nature of these influences seemed to be essential in understanding the mechanism of experimental uremia.

B. THE RELATIONSHIP OF RETENTION OF INORGANIC PHOSPHATE AND CALCIUM ION DEFICIENCY TO UREMIA

A number of observations support the view that diminution in the calcium ion concentration of body fluids is responsible for the increased neuromuscular irritability exhibited in uremia and that this diminution is related to retention of inorganic phosphate: 1. Renal insufficiency is associated with an increase in the inorganic phosphate content of the

serum (de Wesselow [18]). 2. The decline in calcium content of the serum of patients with uremia is greater than that to be expected as a result of coexistent deficiency of plasma protein (Peters and Van Slyke[19]) and is associated with a fall in the ionized fraction (McLean and Leiter [20]). 3. Intravenous injection of solution of alkaline or neutral sodium phosphate produces muscular twitching (Binger [21]). 4. More recent investigations (Hastings [22] and Resnik, Mason, Terry, Pilcher and Harrison [1]) have indicated that diminution in the calcium ions of the tissues of the central nervous system, as evidenced by a deficit in the cerebrospinal fluid, produced by the intracisternal injection of solution of inorganic phosphate, oxalate or citrate, causes muscular twitch-

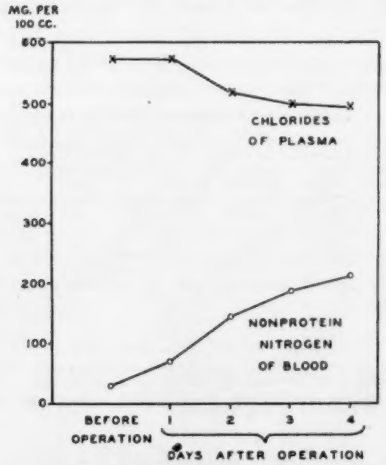

Chart 2.—The average change in six dogs with experimental anuria. The curves illustrate the steady increase in nonprotein nitrogen and the slight diminution in plasma chloride following the onset of anuria.

ing, stertorous breathing and an increase in blood pressure—a syndrome resembling that seen in certain patients with uremia. Similar doses administered intravenously were entirely ineffective, although larger doses produced the same effects after a latent period of from fifteen

18. de Wesselow, O. L. V.: On the Phosphorus and Calcium of the Blood in Renal Disease, Quart. J. Med. **16**:341, 1923.

19. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, Williams & Wilkins Company, 1935.

20. McLean, F. C., and Leiter, L.: The State of Calcium in the Blood in Nephritis and Uremia, J. Clin. Investigation **14**:705, 1935.

21. Binger, C.: Toxicity of Phosphates, in Relation to Blood Calcium and Tetany, J. Pharmacol. & Exper. Therap. **10**:105, 1917.

22. Hastings, A. B.: Personal communication to the authors.

minutes to an hour, as was true in the experiments of Binger.[21] The protocols of Storti's [23] experiments on the effects of intravenous injections of oxalate also indicated a lag in the development of tetany.

These observations suggested that the muscular twitching of uremia produced by calcium ion deficiency may be of central rather than peripheral origin. In order to investigate this the relationships between the symptoms and the alterations in the ionized calcium and inorganic phosphate concentrations of serum and cerebrospinal fluid were investigated in a series of anesthetized dogs [24] after the administration of large intravenous injections of a mixture of primary and secondary sodium phosphate (p_H, 7.4). A typical result is shown in chart 3, which indicates that the onset of twitching was related to decline of the ionized calcium and increase in inorganic phosphate of the cerebrospinal fluid rather than to changes taking place in the serum.[25]

Aside from the muscular twitching the animals receiving intravenous injections of sodium phosphate displayed shivering, tremor, rigidity of the extensor muscles and occasional convulsions. Respiration was usually rapid and frequently stertorous, and in some instances it was of a typically Cheyne-Stokes character. In some of the dogs an exaggerated forcefulness of the heart beat shook the chest. This phenomenon has been observed also in uremic dogs in consequence of experimental anuria.

Observations on a series of nephrectomized dogs indicated that in this condition the onset of twitching is more nearly related to the increase of inorganic phosphate in the cerebrospinal fluid than to the increase in the serum. When sodium phosphate was administered to these nephrectomized dogs, the onset of twitching was hastened; however, the onset still paralleled the rise in the inorganic phosphate, content of the cerebrospinal fluid, rather than that of the serum. Illustrative data for four dogs are given in chart 4.

Studies of the inorganic phosphate, total and ionized calcium contents of serum and cerebrospinal fluid of a series of normal dogs, of dogs in which experimental anuria had been produced shortly before and of dogs which had been anuric three or four days again indicated that the changes in the serum preceded those in the cerebrospinal fluid

23. Storti, E.: Ueber die Frage der Hypocalcämie bei Niereninsuffizienz: Beziehungen zwischen Hypocalcämie und Oxalsäureretention, Ztschr. f. d. ges. exper. Med. **97**:35, 1935.

24. Symptoms in response to the injections of sodium phosphate varied according to the anesthetic employed. The symptoms were most pronounced in unanesthetized animals, least marked in those receiving pentobarbital sodium and intermediate when morphine was used.

25. The intracisternal administration of calcium salts immediately abolished or markedly diminished muscular twitching in dogs with either experimental phosphate intoxication or experimental anuria. The effect would last for several hours.

and that the symptoms of severe renal insufficiency were attended by a decrease in the ionized calcium and an increase in the inorganic phosphate of the cerebrospinal fluid, although some exceptions were noted (table 2).

Comparisons were made also between the inorganic phosphate and ionized calcium contents of the cerebrospinal fluid of patients with renal insufficiency (some of whom had symptoms of uremia) and those of patients without renal disease. These data (table 3) indicate that there tends to be an elevation of inorganic phosphate and a diminution

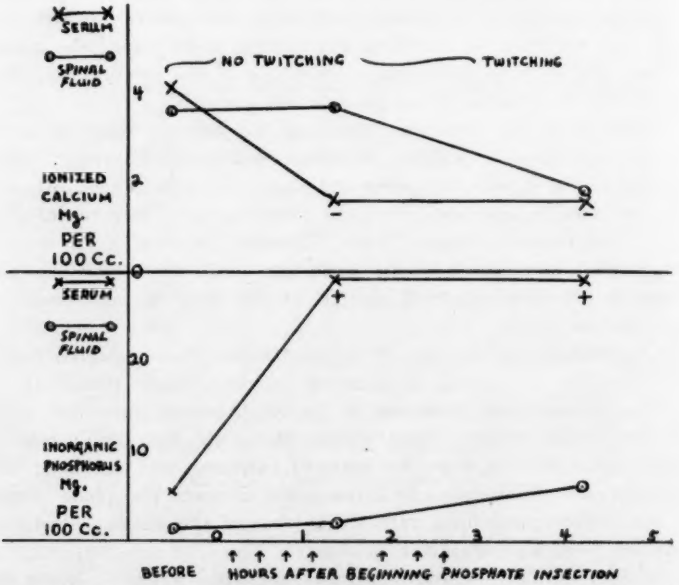

Chart 3.—After the repeated intravenous administration of sodium phosphate (each injection containing 50 mg. of phosphorus per kilogram of body weight), a rapid increase in the phosphate and a decrease in the ionized calcium of the blood were noted, with little or no immediate change in the composition of the cerebrospinal fluid. However, the frequent twitching did not begin until after several hours, at which time the corresponding alterations had begun to be apparent in the cerebrospinal fluid. The onset of twitching appeared to be related to alterations in the cerebrospinal fluid rather than to changes in the blood. Each arrow indicates the intravenous injection of 50 mg. of phosphorus.

of ionized calcium in the cerebrospinal fluid of patients with renal insufficiency.[26]

26. Five patients with renal insufficiency who exhibited increased neuromuscular irritability were given calcium salts intracisternally. In four the twitching was temporarily abolished or markedly diminished by this therapy.

The foregoing data indicate that the occurrence of muscular twitching in experimental uremia is related to a decrease in the calcium ion concentration of the cerebrospinal fluid [27] brought about by the retention of metabolites. It is doubtful if this reduction is to be ascribed entirely to the accumulation of inorganic phosphate, although it tends to parallel this accumulation.[28] It seems likely that the accumulation of oxalate (Becher [3]), citrate or some as yet unknown substances behaving like

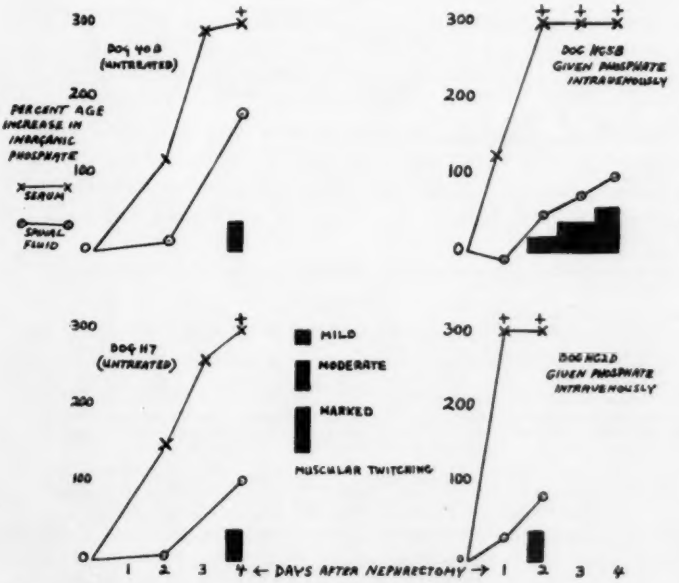

Chart 4.—The two dogs, observations for which are depicted on the right, received daily injections of sodium phosphate (at p_H 7.4). Twitching developed the second day after nephrectomy, while the untreated animals, values for which are depicted on the left, did not display twitching until the fourth day of anuria. In all the animals the onset of twitching appeared to be related to increased concentration of phosphate in the cerebrospinal fluid rather than in the serum.

27. This statement applies only to the increased neuromuscular irritability of the symptom complex of uremia. It does not imply that the tetany associated with calcium deficiency (such as spasmophilia) is of central rather than peripheral origin. We have not studied these conditions.

28. Moderate variations in the concentrations of inorganic phosphate of the standard solutions used in the frog heart assay make no immediate appreciable difference in the calcium ion concentration of these solutions.

citrate plays an augmentative or predominant rôle in suppressing the ionization of calcium.[29]

If it is granted that the composition of the cerebrospinal fluid reflects the composition of the fluid intimately bathing the cells of the central nervous system, a fall in calcium ion concentration of the cere-

TABLE 2.—*Phosphorus and Calcium in Serum and Spinal Fluid of Dogs in Relation to Renal Insufficiency*

Group	Arterial Serum			Cerebrospinal Fluid		
	Inorganic Phosphorus, Mg. per 100 Cc.	Total Calcium, Mg. per 100 Cc.	Ionized Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Total Calcium, Mg. per 100 Cc.	Ionized Calcium, Mg. per 100 Cc.
Normal dogs						
Number of observations	9	5	8	9	10	9
Highest	5.5	11.3	5.0	1.6	5.5	5.1
Lowest	2.9	10.5	3.3	1.1	4.7	3.8
Average	4.0	10.9	4.4	1.3	5.3	4.3
Dogs with early renal insufficiency						
Number of observations	5	3	7	11	5	8
Highest	12.5	12.1	5.0	1.8	6.1	5.0
Lowest	5.9	11.1	1.6	1.2	4.2	3.1
Average	9.6	11.7	3.0	1.5	5.5	4.1
Dogs with renal insufficiency						
Number of observations	6	3	2*	5	4	6
Highest	26.6	12.1	2.8	3.8	6.8	4.9
Lowest	16.6	5.7	2.5	1.7	5.1	0.8
Average	21.7	9.9	2.7	2.5	6.2	3.0

* In most of the animals with severe renal insufficiency the serum had toxic effects on the frog heart, and the amount of ionized calcium could not be satisfactorily measured.

TABLE 3.—*Inorganic Phosphorus, Total Calcium and Ionized Calcium in Cerebrospinal Fluid of Patients With and Without Renal Insufficiency*

Group	Inorganic Phosphorus, Mg. per 100 Cc.				Total Calcium, Mg. per 100 Cc.				Ionized Calcium, Mg. per 100 Cc.			
	Number of Observations	Highest	Lowest	Average	Number of Observations	Highest	Lowest	Average	Number of Observations	Highest	Lowest	Average
Control patients (without renal insufficiency)	20	1.7	0.7	1.3	53	5.5	4.2	4.9	39	5.6	3.5	4.3
Patients with renal insufficiency	16	4.5	0.8	2.7	17	5.6	3.5	4.7	8	4.3	3.3	3.8

29. Tweedy, W. R., and McNamara, E. W.: Effect of Administration of Parathyroid Extract on Serum Calcium Level in the Nephrectomized Rat, Proc. Soc. Exper. Biol. & Med. **35**:414, 1936. These authors have reported that in nephrectomized rats treated with parathyroid extract hypercalcemia does not develop. They have stated the opinion that mobilization of calcium stores is deficient in this condition. This may be another mechanism tending to produce calcium deficiency in the uremic state.

brospinal fluid is indicative of a "central" deficiency of calcium ions. Increase in the inorganic phosphate content of the cerebrospinal fluid appears in many instances to be coincident with the establishment of this deficit.

Exceptions to the relationships just described were frequently encountered. 1. Occasionally dogs exhibited twitching without serious alterations in the levels of ionized calcium and inorganic phosphate in the cerebrospinal fluid.[30] 2. Frequently in the final "depressed" phase of uremia, twitching was absent in spite of considerable diminution in the ionized calcium and large increases in the inorganic phosphate concentration of the cerebrospinal fluid. Indeed, increased neuromuscular irritability frequently preceded the depressed phase at a time when the chemical alterations were much less marked.

Accordingly, it became necessary to search for factors which might call forth motor irritability without depleting the calcium ion concentration and which might inhibit their appearance in spite of an existing "central" deficit of calcium ions.

C. THE RELATIONSHIP OF PHENOL AND RELATED SUBSTANCES TO UREMIA

The inhibiting effects of anesthesia on the twitchings manifested in experimental intoxication due to sodium phosphate suggested that the retention of substances having a narcotic action might account for the absence of neuromuscular irritability in spite of a "central" deficit of calcium ions. The extensive researches of Becher[31] have furnished strong evidence that the constant occurrence of apathy and weakness in the earlier phases of uremia and the frequent development of stupor and coma in the later phases are consequences of the retention of free phenols. We have therefore undertaken experiments to elucidate further the relationship of these compounds to the symptom complex of uremia.

Experimental Phenol Intoxication.—After the intravenous injection of nonlethal doses of phenol and paracresol into dogs a characteristic syndrome develops. Swimming movements are immediately displayed. These are followed by tremor and salivation, lasting several minutes. As these manifestations subside, weakness and apathy, with marked ataxia, are noted.

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30. Salvesen, H. A.: Die Beziehungen zwischen den urämischen Muskelzuckungen und den pathologisch-chemischen Blutbefunden, Ztschr. f. klin. Med. **115**:522, 1931. Peters, J. P.: Salt and Water Metabolism in Nephritis, Medicine **11**:435, 1932. These authors have shown that muscular twitching may occur in patients with uremia in the absence of outspoken elevation of the inorganic phosphate content of the serum.

31. Becher, E.: Studien über die Pathogenese der echten Urämie, Zentralbl. f. inn. Med. **46**:369 (April 25) 1925.

A somewhat similar syndrome is produced by the intraperitoneal injection of phenol and paracresol into mice. Tremor appears in a few minutes, along with weakness and stupor, the latter lasting for an hour or longer after the tremor has disappeared. When minimal lethal doses are administered, death may not occur for twelve hours or more. During this time the mouse lies on its side, unable to move and barely responsive to stimuli, apparently in a comatose state. Section of the kidneys of these mice have shown well marked renal damage, especially tubular degeneration.

These findings support the views of Becher, who has claimed that phenol retention as a result of renal disease tends to aggravate further the underlying disorder of the kidneys. According to Becher, chronic phenol poisoning in man produces a syndrome characterized by fatigue, emaciation, sleeplessness, weakness, hypothermia and finally stupor. He has emphasized the fact that the free phenol content of the blood of certain nephritic patients may be as high as that of patients with chronic phenol intoxication.

The Effect of Phenol on the Response to Intracisternally Injected Inorganic Phosphate.—The syndrome produced by the intracisternal injection of substances tending to reduce the calcium ion concentration of the fluid bathing the central nervous system, such as phosphate, oxalate and citrate, has been described by Resnik, Mason, Terry, Pilcher and Harrison.[1] Similar injections of sodium phosphate were made after the administration of paracresol either intracisternally or intravenously. The usual manifestations of twitching, respiratory stimulation and increase in blood pressure were completely inhibited. Typical results are illustrated in chart 5.

The Phenol Content of Blood and Cerebrospinal Fluid of Dogs With Experimental Anuria.—The results of observations made on normal dogs and dogs with experimental anuria of from two to four days' duration are given in table 4. Data on the phenol content of the blood of patients are found in table 5. It is evident that the concentration of phenol in body fluids is increased in states of renal insufficiency. The procedure we have employed for determining the phenol content[14] is not highly specific and probably determines a number of other substances, such as diphenols, dioxybenzenes, oxyacids and related compounds, as well as free phenols; however, Becher[31] has obtained similar results using an apparently more specific method.

Because the phenol content of body fluids is increased in uremia and because it has been shown that experimental phenol intoxication in animals and chronic phenol intoxication in man[3] are characterized by symptoms of depression and narcosis closely simulating certain symptoms of the uremic complex, it seems likely that instances of uremia lacking

in increased neuromuscular irritability in spite of "central" deficit of calcium ions are to be explained on the basis of the antagonistic action of retained phenols. This concept is materially strengthened by the experimental demonstration of the antagonistic action which has been described.

D. THE RELATION OF GUANIDINE[32] TO UREMIA

The manifestations of increased motor irritability in uremia are occasionally encountered both clinically and experimentally in the absence of evidence of an existing deficiency of calcium ions, e. g., when the inorganic phosphate content of the serum is only slightly elevated

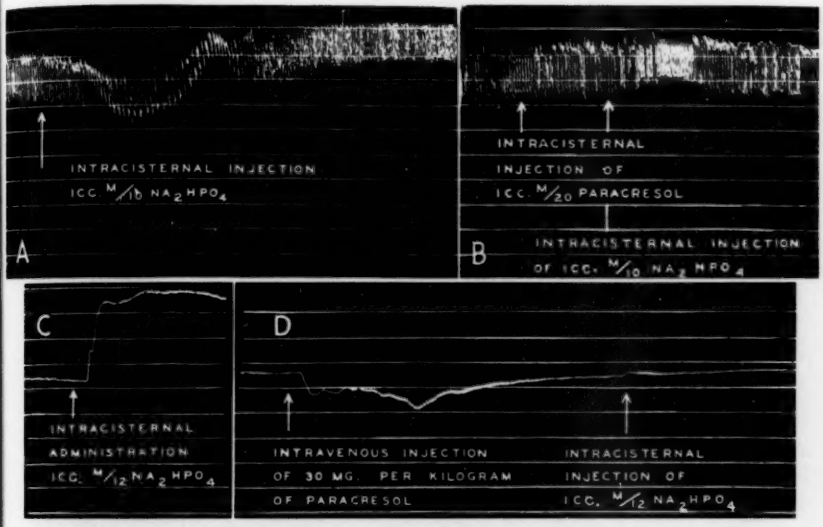

Chart 5.—The curves pass from left to right. The distance between adjacent horizontal lines designates 20 mm. of mercury. *A*, the intracisternal administration of disodium hydrogen phosphate caused an increase of approximately 30 mm. of mercury. *B*, after the blood pressure had returned to the control level, paracresol was injected intracisternally and followed by disodium hydrogen phosphate. Only the slightest increase in blood pressure occurred. *C*, in another dog a rise of 70 mm. in blood pressure was produced by phosphate. *D*, the same compound, when injected after the intravenous administration of paracresol, had practically no effect.

32. Study of the significance of guanidine in health and in disease has been hampered by lack of specific methods for the determination of this substance in body fluids. In this paper "guanidine" will designate the substance or substances giving the Sakaguchi, or nitroprusside, reactions, and guanidine will be reserved for the organic base itself.

and that of the cerebrospinal fluid is within normal limits. In these instances the twitchings must be initiated by a different mechanism, and there is some evidence that guanidine and/or its derivatives are important factors in the production of these and certain other signs of the uremic complex: 1. Foster [33] isolated from the serum of certain patients with uremia a toxic organic base which caused twitching, rapid breathing, convulsions and death when injected into guinea-pigs. The chemical properties of this substance suggest that it was guanidine or a guanidine derivative. 2. Several observers (Pfiffner and Meyers,[34] de Wesselow and Griffiths,[35] Bohn and Schlapp [36] and Kleeberg and Schlapp [37]) have observed increases in the "guanidine" content of the

TABLE 4.—*Free Phenols* of the Blood and Cerebrospinal Fluid of Normal Dogs and Dogs with Renal Insufficiency*

Material Analyzed	Normal Dogs		Dogs with Experimental Anuria	
	Number of Observations	Free Phenols, Mg. % (Average Value)	Number of Observations	Free Phenols, Mg. % (Average Value)
Blood	6	3.7	16	8.0
Cerebrospinal fluid	5	2.0	9	6.6

* The method used measures not only phenols but certain related compounds.

TABLE 5.—*Guanidine and Phenols in the Blood of Patients With and Without Renal Insufficiency*

Group	Guanidine, Mg. per 100 Cc.				Free Phenols, Mg. per 100 Cc.			
	No. of Observations	Highest	Lowest	Average	No. of Observations	Highest	Lowest	Average
Control patients (without renal insufficiency)	12	0.48	0.32	0.40	10	4.6	2.3	3.1
Patients with renal insufficiency	9	6.48	0.44	2.09	12	9.6	2.5	6.3

33. Foster, N. B.: The Isolation of a Toxic Substance from the Blood of Uremic Patients, Tr. A. Am. Physicians **30**:20, 1915.

34. Pfiffner, J. J., and Meyers, V. C.: Colorimetric Estimation of Methylguanidine in Biological Fluids, Proc. Soc. Exper. Biol. & Med. **23**:830, 1926; On Colorimetric Estimation of Guanidine Bases in Blood, J. Biol. Chem. **87**: 345, 1930.

35. de Wesselow, O. L. V., and Griffiths, W. J.: Blood Guanidine in Hypertension, Brit. J. Exper. Path. **13**:428, 1932.

36. Bohn, H., and Schlapp, W.: Untersuchungen zum Mechanismus des blassen Hochdrucks: Der Guanidingehalt des Blutes beim blassen und roten Hochdruck, Zentralbl. f. inn. Med. **53**:571, 1932.

37. Kleeberg, J., and Schlapp, W.: Ueber die Auffindung von urämieerzeugenden Stoffen, Ztschr. f. physiol. Chem. **188**:81, 1930.

blood of some (but not all) patients with renal insufficiency. 3. Administration of guanidine produces under certain conditions a symptom complex closely resembling that of uremia. For these reasons certain experiments were performed in order to elucidate further the rôle of guanidine in the uremic state.

Experimental Guanidine Intoxication.—The clinical picture produced by the experimental administration of guanidine in a large series of dogs was found to depend on dosage, site of injection and kind of anesthetic employed. In unanesthetized dogs small doses given intravenously usually cause a fall in blood pressure, while intracisternal administration causes a rise in blood pressure. The duration of the pressor effect is brief. Toxic doses administered subcutaneously are followed after about an hour by salivation, apathy, vomiting, retching and diarrhea. Incoordination, ataxia and fibrillary tremors followed by clonic twitching and convulsions are commonly observed. When larger doses are given, the phase of nervous hyperirritability may pass rapidly into one of profound depression, in which the animal lies in a semicomatose state from which he can be aroused only with difficulty. For the first hour after the injection the blood pressure remains unchanged or falls slightly. During the second hour a definite rise occurs (30 to 40 mm. of mercury) and is maintained for three or four hours, followed by a fall to normal or subnormal levels as the intoxication becomes more profound. If the dose used produces a fatal termination, this drop in blood pressure is progressive, the animal dying after a period of circulatory collapse of variable length. At autopsy evidence of marked peripheral capillary damage is encountered. Patchy hemorrhagic gastroenteritis is a constant finding. The circulatory features of guanidine have been studied by Minot.[38]

We have confirmed the observation of Major and Weber [39] that after the intravenous injection of a large dose of guanidine or methyl guanidine into an anesthetized dog, there is a prompt elevation in blood pressure which may be sustained for an hour or longer. Doses too small to be effective intravenously were found to be markedly pressor when injected into the cisterna magna, indicating that guanidine has a "central" action, in addition to the peripheral pressor effect which was demonstrated by Goldblatt and Karsner.[40]

The "Guanidine" Content of the Blood and Cerebrospinal Fluid of Dogs with Experimental Uremia.—The data obtained for uremic dogs

38. Minot, A. S., and Keller, M.: Circulatory Failure Associated with Guanidine Intoxication, J. Pharmacol. & Exper. Therap. **60**:32, 1937.

39. Major, R. H., and Weber, C. J.: Possible Increase of Guanidine in Blood of Certain Persons with Hypertension, Arch. Int. Med. **40**:891 (Dec.) 1927.

40. Goldblatt, H., and Karsner, H. T.: Site of Pressor Action of Dimethylguanidin Sulfate, J. Pharmacol. & Exper. Therap. **47**:247, 1933.

are shown in table 6.[41] Because of the difficulty in obtaining sufficient material, only a few observations were made on cerebrospinal fluid. It is seen that the "guanidine" content of the blood is markedly increased and that appreciable quantities occur in the cerebrospinal fluid of dogs in the uremic state. Similar results have been obtained for patients with renal insufficiency (table 5).

The Significance of Guanidine in Uremia.—Until more specific chemical methods demonstrate that the increased color reaction in uremic fluids is due to guanidine itself or to pharmacologically similar derivatives, it is not justifiable to assign this substance a definite rôle in the pathogenesis of the syndrome. That it may be important is suggested by the following facts: 1. Experimental guanidine intoxication produces vomiting, diarrhea, gastro-enteritis, muscular twitching, increases in

TABLE 6.—*Studies of Guanidine Values for Uremic Dogs*

Number	Cause of Uremia	Mg. per 100 Cc. of Blood		Mg. per 100 Cc. of Cerebrospinal Fluid, Guanidine
		Nonprotein Nitrogen	Guanidine	
43	Ligation of renal arteries	200	1.76	....
41	Ligation of renal arteries	73	0.61	....
		130	0.76	....
Hg2	Ligation of renal artery	211	5.80	....
H7	Bilateral nephrectomy	158	3.45	....
40B	Bilateral nephrectomy	176	5.60	....
Hg5	Ligation of both ureters	113	2.50	....
		254	5.88	
Hg1D	Ligation of both ureters	400	8.15	1.41
Hg1E	Nephrectomy	183	7.59	1.70
Hg10	Bilateral nephrectomy	176	....	Trace
Hg2B	Ligation of both ureters	153	....	0.43
73	Nephrectomy	45	1.01	....

blood pressure and respiratory disturbances and in advanced stages apathy, stupor and circulatory collapse. These features are encountered also as a part of the symptom complex of uremia. 2. Guanidine behaves as the physiologic antagonist of calcium, and the nervous features of guanidine poisoning either in the intact animal or in the isolated muscle-nerve preparation can be inhibited by adequate amounts of calcium salts.[42] Animals in a deficient state of nutrition in respect to calcium are more susceptible to guanidine intoxication; on the other hand, inten-

41. The "guanidine" content of the blood of normal dogs as determined by the Minot and Dodd method is usually less than 0.4 mg. per hundred cubic centimeters, the spinal fluid containing no detectable amount. In analyses of fluids during uremia the color value of urea, uric acid and creatinine is compensated by adding similar amounts to the standard.

42. Minot, A. S., and Cutler, J. T.: Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, J. Clin. Investigation **6**:369, 1928. Kühnau, J., and Nothmann, M.: Ueber die Guanidintoxikose und ihre Beziehungen zur Tetanie, Ztschr. f. d. ges. exper. Med. **44**:505, 1924-1925.

sive calcium therapy will prevent the capillary damage, effects on carbohydrate metabolism and changes in blood pressure otherwise resulting from the administration of guanidine. 3. Salvesen [43] has pointed out that vomiting is usually the initial uremic symptom and may occur in persons without disturbances of the serum electrolytes and with only minimal elevations of the urea content of the blood, therefore at a time before any serious degree of gastro-intestinal irritation could be expected from the ammoniacal fermentation of urea—a mechanism suggested by Becher [3] and supported by the experimental evidence of Hessel and Pekelis.[44] Vomiting is, however, an early feature of guanidine intoxication.

These facts support the hypothesis that guanidine may be responsible for the twitching observed in uremia when there is no evidence of "central" deficit of calcium ions. In the presence of a deficit the effects of guanidine are enhanced. It is further suggested that the early symptoms of gastro-intestinal irritation may be initiated and that the later symptoms of depression and collapse may be augmented by accumulation of this toxic organic base and/or its derivatives.

E. THE RELATION OF UREA TO UREMIA

The available evidence (Fishberg [2]) indicates that the amounts of urea accumulating in body fluids in uremia are insufficient to induce a primary toxic action. Nevertheless, retention of urea may facilitate the development of the uremic state in several ways: 1. The effects of dehydration are augmented (Peters and Van Slyke [19]). 2. The osmotic pressure of bloody fluids is increased, a point stressed by von Korányi,[45] 3. Becher [3] has claimed that bacterial decomposition of urea to ammonia in the alimentary tract is an important cause of stomatitis, gastritis and colitis. This hypothesis has been supported by Hessel and Pekelis,[44] who found that there was from 200 to 300 mg. of ammonia per hundred cubic centimeters in the fluid from gastric fistulas of nephrectomized dogs and that when this material was constantly drained the damage to the mucosa of the tract below the fistula

43. Salvesen, H. A.: Vomiting of Uremia and Its Relation to Pathochemical Blood Findings, Acta med. Scandinav. **81**:406, 1934.

44. Hessel, G., and Pekelis, E.: Untersuchungen über die Ausscheidung harnfähiger Stoffe in den Magendarmkanal bei nephrektomierten Hunden: Ein Beitrag zur Frage der sog. vikariierenden Sekretion; Die Bedeutung der harnpflichtigen Stoffwechselschlacken in den Verdauungssäften für das Krankheitsbild und den Verlauf der Urämie, Ztschr. f. d. ges. exper. Med. **91**:331, 1933.

45. von Korányi, A.: Physiologische und klinische Untersuchungen über den osmotischen Druck thierischer Flüssigkeiten, Ztschr. f. klin. Med. **33**:1, 1897; Klinische Thier, ibid. **34**:1, 1898.

was in each case considerably less than it otherwise would have been. 4. Becher and also Fishberg [2] have suggested that urea retention may inhibit the normal metabolism of precursors of urea, some of which may be toxic. This hypothesis has not, to our knowledge, been experimentally tested.

On the assumption that retention of urea might interfere with the normal rate of detoxication or decomposition of toxic substances, themselves not necessarily precursors of urea, we have observed the effects of elevation of the urea content of body fluids on the rate of disappearance of injected guanidine. A series of dogs were given equivalent doses of guanidine (25 mg. per kilogram intravenously). A second series of dogs were given large intravenous injections of urea (2 Gm. per kilogram) just prior to administration of guanidine. The "guanidine"

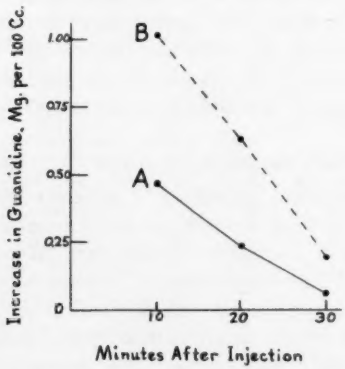

Chart 6.—The procedure was exactly the same in all the animals except that one series (*A*) received guanidine only while the other group (*B*) were given urea also. The rate of disappearance from the blood of the injected guanidine was much slower in the latter animals. *A*, the average values for four dogs after the intravenous administration of 25 mg. of guanidine hydrochloride per kilogram. *B*, the average values for four dogs after the administration of 25 mg. of guanidine hydrochloride plus 2 Gm. of urea per kilogram. This graph shows the retarding influence of urea on the disposal of injected guanidine in normal dogs.

content of the blood was then followed at intervals for thirty minutes. The results of these experiments (chart 6) indicate that the presence of urea delays the disappearance from the blood stream of administered guanidine. Little is known of the fate of injected guanidine. There is evidence, however, that some is excreted as such in the urine, some is transformed into creatine and some is destroyed by unknown paths. Which aspects of utilization of guanidine are interfered with by urea

cannot be stated, but it is unlikely that urinary excretion is hampered. It is felt that in renal insufficiency the elevation of blood urea may augment the accumulation of "guanidine" in body fluids.[46]

F. DISTURBANCES IN ACID-BASE AND FLUID BALANCE OF BLOOD AND CEREBROSPINAL FLUID IN RELATION TO UREMIA

A good deal of evidence supports the conclusion that disturbances in acid-base and fluid balances in uremia are augmentatory influences which when present are of grave importance in respect to the condition of the uremic subject but which may be absent in spite of outspoken uremia. This point of view has been discussed in detail by Harrison and Mason.[8]

In a study of dogs with experimental uremia observations of the acid-base balance of serum and cerebrospinal fluid were made. It

TABLE 7.—*Acid-Base Condition of Serum and Cerebrospinal Fluid of Dogs in Relation to Experimental Anuria*

	Arterial Serum			Cerebrospinal Fluid		
Group	p_H	Carbon Dioxide Content, Vol. %	Carbon Dioxide Tension, Mm. of Mercury	p_H	Carbon Dioxide Content, Vol. %	Carbon Dioxide Tension, Mm. of Mercury
Average values for four normal dogs	7.49*	50.4	30.1*	7.42	54.4	40.2
Average values for four dogs with anuria of three days' duration	7.38	26.7	20.2	7.40	55.3	46.3

* The low values for carbon dioxide tension and the high values for p_H for the normal animals can probably be explained by the fact that the experiments were carried out in the summer and most of the animals were panting when samples were taken.

was noted that in dogs with rapidly developing renal insufficiency there was a surprising lag in the extension of the depletion of alkaline reserve, as indicated by findings in the serum and in the cerebrospinal fluid, and in the presence of severe uncompensated acidosis the findings in the cerebrospinal fluid were within normal limits. The results are given in table 7. Comparative studies of acid-base balance in serum and cerebrospinal fluid in states of renal insufficiency by others have produced contradictory results. The literature has been summarized by Katzenelbogen.[47]

46. Observations were made on the effects of injections of the ethereal sulfate derivative of paracresol on the rate of disappearance of injected phenols from the blood stream. The results indicated that there was some diminution in the rate of disappearance of free phenol and paracresol under these conditions. Injections of urea with phenol or paracresol did not augment or diminish their toxicity. The effect of urea on the rate of disappearance of injected phenols was not studied.

47. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

G. THE EFFECT OF UREMIC SERUM ON THE FROG HEART

Evidence of the multiplicity of factors which may play a rôle in the production of the uremic syndrome is obtained from a study of the effects of serum from dogs with renal insufficiency on the isolated frog heart used in the determination of ionized calcium by the method of McLean and Hastings.[13]

The application of this method to the serum of normal dogs is hindered by augmentor effects which have no relation to the calcium ion concentration. Human serum, on the other hand, rarely is disturbing in this respect. The serum of dogs with experimental anuria of three or four days' duration commonly exerted one of two bizarre effects, aside from augmentation, on perfusion of the frog ventricle. In a number of instances diastolic arrest occurred promptly (chart 7). The substance

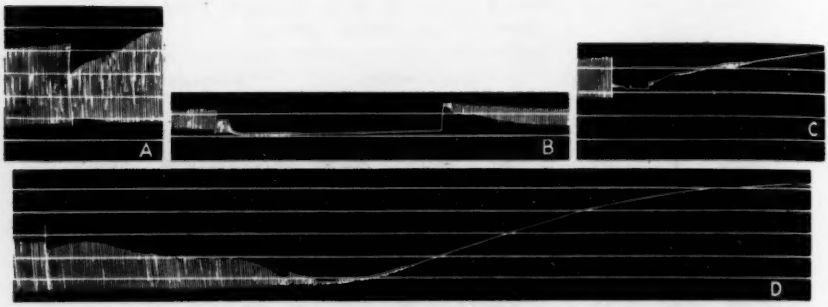

Chart 7.—The records were obtained from the hearts of frogs, the upstrokes indicating systole. At the beginning of each curve the cannula in the heart contained Ringer's solution. Replacing this liquid with serum from uremic dogs caused several different effects: simple augmentation (*A*), diastolic arrest (*B*), which disappeared when the serum was replaced by Ringer's solution, and systolic arrest (*C*). The lower curve (*D*), illustrates all three effects from a single injection of serum.

responsible for this was found to be soluble in alcohol and ether and dialyzable. Phenol and paracresol added to the perfusion liquids were found to produce a similar effect. The most striking and common result was the production of systolic standstill (chart 7). This effect usually came on slowly, occasionally rapidly, and persisted for hours after replacement of the serum by the usual stock perfusion liquids. Although the ventricle was firmly contracted the auricle usually continued to beat. Attempts to study the chemical properties of the substance having this digitalis-like action were unsuccessful, largely because of the instability of the substance and the limitations of the frog heart method. It disappeared from serum in a few hours at room temperature and after a

day or two in the icebox. It was not recovered from serum ultrafiltrates. None of the commonly known substances retained in renal insufficiency had this effect. Whether this substance plays any rôle in the production of the uremic state in dogs cannot, of course, be stated. It is of interest that similar effects were occasionally produced also by serum from patients with uremia.

H. CHANGE IN BLOOD PRESSURE IN RELATION TO UREMIA

Of twelve bilaterally nephrectomized animals, two displayed a rise in blood pressure; in nine of the remaining ten animals a diminution in blood pressure occurred some time after the operation. The increase,

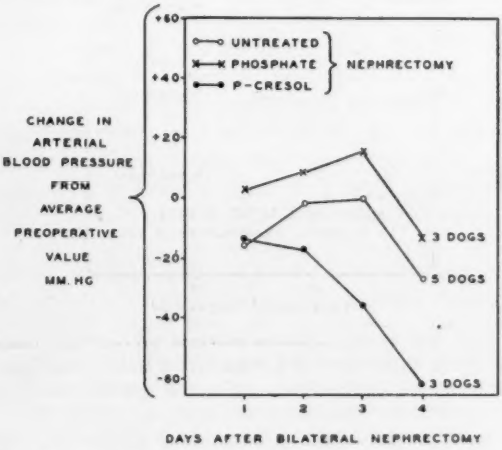

Chart 8.—Each curve represents the average value for the blood pressure of three nephrectomized dogs. Those receiving daily injections of phosphate had the highest blood pressure, and those given paracresol the lowest, the untreated animals showing intermediate values.

when it occurred, was usually observed on the second or third postoperative day, while the most marked decline occurred after four or five days of anuria, when the animals were moribund. Since, as has been pointed out (chart 5), the intracisternal administration of phosphate causes a rise in blood pressure which can be prevented by the previous injection of free phenol, since guanidine intoxication may cause either an increase or a decrease in blood pressure, depending on the state of the animal and the dose of the compound, and since dehydration as the result of vomiting tends to cause a fall in blood pressure, it appears that the changes in the blood pressure in the anuric dog are the resultant of the interaction of several factors. Further evidence

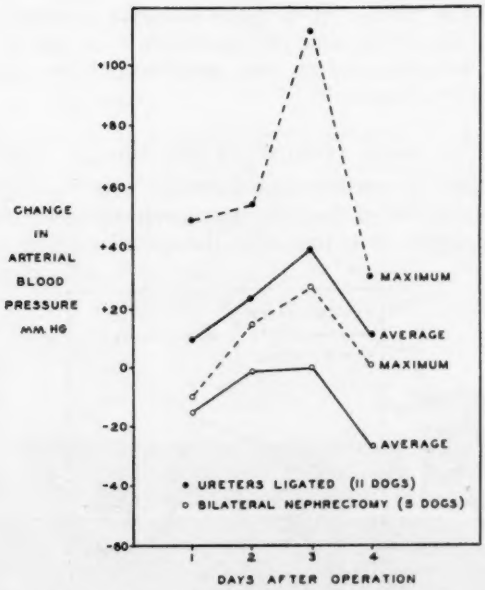

Chart 9.—Maximal and average changes in blood pressure are compared in dogs subjected to double nephrectomy and those having both ureters ligated. The latter dogs tended to have hypertension, while the former usually displayed either no change or a decline in blood pressure.

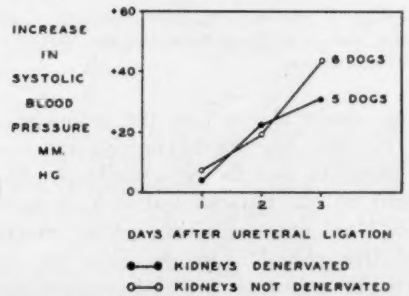

Chart 10.—Denervation of the kidney had no significant effect on the rise in blood pressure produced by ligation of both ureters.

on this question was obtained by comparing the changes in blood pressure in three groups of nephrectomized animals, one group receiving daily intravenous injections of inorganic phosphate, a second receiving injections of phenol and the third being untreated. As shown in chart 8, the first group tended to have some increase in blood pressure, the second showed a well marked decline and the untreated nephrectomized animals showed an intermediate pressure.

After ligation of both ureters a distinct increase in blood pressure occurred in most of the animals on the second and third postoperative days. The degree of this change was variable, being as much as 100 mm. in some dogs and not beyond the experimental error in others. On the average, however, these animals displayed a distinctly greater rise in blood pressure than did the nephrectomized dogs (chart 9). Since anuria was complete in both groups, the difference in response cannot be ascribed to retention products. In addition to the agents mentioned in the preceding paragraph, it appears that some other factor more specifically related to the presence in the body of abnormally functioning renal tissue must have been concerned in the production of the elevation in blood pressure following bilateral ureteral ligation. Such a pressor influence from the kidney might theoretically be exerted either by chemical or by "nervous," i. e., reflex, routes. The latter possibility is rendered unlikely by the fact that denervation of the kidneys had little or no effect on the rise in blood pressure produced by ureteral ligation (chart 10). Our experiments throw no light on the question as to whether this hypothetic chemical agent acts directly on the vessels or indirectly by way of the nervous system. In any case, it seems clear that while retention products may exert a slight influence in elevating the blood pressure, the chief factor in "renal" hypertension is some functional disturbance of the kidney other than that which leads to the accumulation of waste products in the body.

COMMENT

Numerous attempts to relate the symptoms of the uremic syndrome to accumulation of a single toxic substance have failed to receive clinical or experimental substantiation. These unitary theories of uremia have been discussed in detail elsewhere (Fishberg [2] and Harrison and Mason [4]). The available evidence indicates that the symptom complex is the summated expression of a number of interplaying factors, each of which in the last analysis is the result of the underlying disorder of function—failure to excrete the end-products of metabolism. Granting the incompleteness of the present knowledge, the experiments which have been described permit the drawing of certain generalizations concerning the mechanism of experimental uremia.

"Central" deficit of calcium ions appears to be an important cause of increased neuromuscular irritability. This deficit is brought about by accummulation of substances forming relatively unionized calcium salts. Retention of inorganic phosphate is important not only in this respect but also as a convenient indicator of the extent of the process. The fact already cited, that both in experimental phosphate intoxication and in experimental anuria twitching parallels the rise in inorganic phosphate and the fall in ionized calcium of the cerebrospinal fluid rather than similar changes in the serum, points to the nervous stimulation as being central rather than peripheral. In these dogs, as well as in patients with uremia, twitching is abolished by the intracisternal administration of calcium salts in amounts completely ineffective intravenously. The lag in development of changes in ionic pattern of the cerebrospinal fluid would probably be less marked in slowly developing renal insufficiency.

The same mechanism may play a minor rôle in the production of respiratory disturbances and of increase in blood pressure, both symptoms being produced by the intracisternal injection of phosphate, oxalate and citrate.

In many instances, however, twitching is absent in spite of evidence of "central" deficit of calcium ions or present when there is little evidence of such a deficit. Other mechanisms are therefore involved.

Accumulation of phenol derivatives appears to be an important factor in the production of weakness, apathy, stupor and coma, i. e., the depressed phase of uremia. A rough parallelism exists between the amounts of these substances in the blood and the degree of apathy. Administration of free phenols to experimental animals produces stupor; administration to nephrectomized animals accelerates the development of weakness and apathy. In addition, the muscular twitching and increase in blood pressure arising from "central" deficit of calcium ions established by the intracisternal injection of phosphate may be completely inhibited by previous administration of phenol, either intravenously or intracisternally. It is believed, therefore, that when neuromuscular stimulation is absent, in spite of "central" deficiency of calcium ions, the inhibition is an expression of the pharmacologic action of retained phenols.

The uremic organism is to be thought of as being subjected to two major antagonistic influences—stimulation and depression. Additional factors, however, are concerned in this balance. Most of the important symptoms of uremia can be produced experimentally by guanidine intoxication, although the symptoms depend on the dose, route of administration and type and depth of anesthesia. It seems likely (although not proved conclusively) that the "guanidine" accumulating in body fluids during uremia is guanidine and/or its derivatives. It is

inferred, therefore, that guanidine, the physiologic antagonist of calcium, may be responsible for increased neuromuscular irritability in those instances in which there is no evidence of calcium ion deficit. On the other hand, extreme degrees of guanidine accumulation may well augment the symptoms of apathy and stupor, such as occasionally occur with minimal phenol retention. Guanidine probably plays a part also in the development of vomiting, diarrhea and gastro-enteritis occurring in the uremic state.

The "nervous" manifestations of uremia are, then, to be thought of as resultants of two opposing influences. "Central" deficit of calcium ions tends to cause irritative phenomena, whereas accumulation of phenol derivatives favors exhibition of apathy, weakness and stupor. The clinical picture depends on which is in ascendency, and accordingly one may observe twitching and convulsions or weakness and stupor or alternations and combinations of these states. This balance is further complicated by the influence of "guanidine" bodies which, depending on conditions, may produce either manifestations of irritation or depression.

The available evidence indicates that retention of urea, the cardinal sign of renal insufficiency, is only indirectly embarrassing to the organism. Ammonium salts, formed by bacterial decomposition of urea in the alimentary tract, augment gastro-intestinal irritation. Evidence has been discussed indicating that high concentrations of urea interfere with the disposal of guanidine by the body.

The increase in blood pressure often encountered in experimental uremia may be brought about in part by overactivity of the medullary centers as a result of deficiency of calcium ions.[48] This mechanism ordinarily is of little import, and the hypertension is related to the presence in the organism of abnormally functioning renal tissue rather than to retention of normal urinary constituents. This view is supported by the observations showing that bilateral ureteral ligation in dogs produces a greater and more constant hypertension than does bilateral nephrectomy.

Some evidence has been gained that accumulation of conjugated phenols inhibits the further detoxication of free phenols. Further investigations of the detoxifying functions of the kidney, liver and gastro-intestinal canal in states of renal insufficiency are needed. It is possible that the similarities between the clinical picture of advanced hepatic insufficiency and the depressed phase of uremia may be consequences of the same mechanism—failure to detoxify or otherwise dis-

48. Patients in whom uremia develops frequently display a slight or moderate increase in blood pressure (usually superimposed on already existing hypertension) not referable to the onset of congestive heart failure. Intracisternal injections of calcium salts in several instances abolished this increment of hypertension.

pose of certain poisonous products of the intermediary metabolism of tissues or bacterial action in the intestines.

The factors which have been mentioned are probably not the only ones responsible for the uremic syndrome, and many still unknown influences may be operative. In certain instances dehydration, greatly increased protein catabolism and base and chloride deficit, with acidosis, appear to be of no little import; however, while these disturbances often augment the development of uremia, they are not essential features of the symptom complex, and all may be absent in occasional instances.

SUMMARY

The uremic syndrome produced in dogs by bilateral nephrectomy resembles that brought about by ligation of both ureters except that a rise in blood pressure is more likely to follow the latter procedure.

The manifestations of increased neuromuscular irritability of anuric dogs are believed to be dependent on the retention of substances having an antagonistic action—either chemically or pharmacologically—to ionized calcium. Since these manifestations tend to parallel the deficit of calcium ions in the cerebrospinal fluid rather than that in the serum, it is believed that they are mediated centrally.

The depressed phenomena of uremia are ascribed to the retention of phenolic bodies.

Variations in the nervous manifestations of anuric dogs are believed to be dependent on the balance between opposing factors—those tending to produce irritative phenomena and those leading toward depression.

Investigations of the guanidine content of the body fluids of uremic organisms and studies of experimental guanidine intoxication indicate that this compound may play an important rôle in the production of some of the clinical features of the syndrome.

Data have been presented which indicate that disturbance of acid-base balance, retention of urea and accumulation of substances as yet unidentified also play a rôle.

On the basis of these observations a hypothesis has been outlined which accounts for the chief features of the uremic syndrome.

Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF CURRENT LITERATURE

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PHILADELPHIA

Notable advances of academic and practical value have been reported during the past year, especially with regard to the more common infections. A new form of antipneumococcus serum has been proposed, and, according to reports, chemotherapy in certain streptococcic and colon bacillus infections has at last attained a modicum of success. Information in regard to the etiology of influenza has been clarified, and further advances have been made in the highly important field of the "crystalline viruses."

PNEUMONIA

Judging from the number of studies published during the past year, recognition of the importance of regarding pneumonia from an etiologic point of view, as advocated for more than twenty years by Cole, has finally become general. The subject is excellently reviewed by Cole [1] in several articles. Further evidence of the interest in this most important of infectious diseases is the organization of special campaigns or commissions for its study and control in many states and cities, lately in Pennsylvania, Minnesota, Ohio and Maryland. The plan of the campaign in the state of New York is outlined by Rogers.[2] During the past year a number of important papers have appeared on the treatment with specific serum of pneumonia caused by various types of pneumococci.

Type I Infections.—Cecil [3] points out that all the recent reports dealing with the therapeutic effectiveness of Felton's concentrated serum without exception have been favorable. He reemphasizes the impor-

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1. Cole, R.: Recent Advances in the Control of Pneumonia, Am. J. Pub. Health **26**:1191-1197 (Dec.) 1936; The Treatment of Pneumonia, Ann. Int. Med. **10**:1-13 (July) 1936; Pneumonia, New York State J. Med. **36**:1699-1709 (Nov. 15) 1936.

2. Rogers, E. S.: The New York State Program for the Control of Pneumococcus Pneumonia, Am. J. Pub. Health **27**:133-141 (Feb.) 1937.

3. Cecil, R. L.: Effects of Very Early Serum Treatment in Pneumococcus Type I Pneumonia, J. A. M. A. **108**:689-692 (Feb. 27) 1937.

tance of giving specific antiserum early in the illness. The disease may in fact be completely aborted if treated early enough, as I have also noted in my own experience. Cecil collected reports of 160 cases in which treatment was given in the first twenty-four hours of illness. Only 8 deaths occurred, making a remarkably low mortality rate of 5 per cent, as compared with from 20 to 25 per cent in cases in which treatment with serum was not given. No complications occurred in his series of 37 cases. Benjamin, Blankenhorn and Senior [4] in 50 cases of infection due to type I pneumococci gave treatment early in the disease, and in no case did death occur. Abernethy [5] reports 25 consecutive cases in which serum was given, with no deaths and no serious complications. He found it possible to regulate the dose of serum by use of the cutaneous test with type I polysaccharide. The average number of units given was 335,000. About 200,000 units was necessary in the average case in which there was no complication. Finland [6] found that 75,000 units was adequate early in the disease, but he recommends giving 150,000 units when more than one lobe is involved and 250,000 or more units if culture of the blood gives a positive result. He found the most frequent causes for failure of serum treatment to be (*a*) error in typing, (*b*) insufficient doses or spread of doses over too long an interval, (*c*) beginning focal complication, (*d*) mixed infection in the lungs, (*e*) other complicating factors and diseases, (*f*) errors in estimating the time of onset of the disease and (*g*) the extent of the pulmonary lesion. Another analysis [7] of failure of serum treatment in 44 cases shows that the chief causes were: (*a*) the advanced age of the patient, (*b*) the delay in giving serum, (*c*) the inadequate doses of serum, (*d*) the severe anoxemia and (*e*) the presence of complications or other diseases.

The mortality rate for rats infected with type I pneumococci was reduced by treatment with sulfanilamide.[7a] Clinical tests made elsewhere, but not reported on as yet, were disappointing.

4. Benjamin, J. E.; Blankenhorn, M., and Senior, F. A.: The Results of the Treatment of Pneumonia with Specific Therapeutic Serum, Ohio State M. J. **33**:36-42 (Jan.) 1937.

5. Abernethy, T. J.: Concentrated Antipneumococcus Serum in Type I Pneumonia, New York State J. Med. **36**:627-635 (April 15) 1936.

6. Finland, M.: Adequate Dosage in the Specific Serum Treatment of Pneumococcus Type I Pneumonia, Am. J. M. Sc. **192**:849-865 (Dec.) 1936.

7. Rosenblüth, M. B., and Block, M.: Pneumonia Due to Type I Pneumococcus, Arch. Int. Med. **58**:102-116 (July) 1936.

7a. Gross, P., and Cooper, F. B.: *P*-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infection of Rats, Proc. Soc. Exper. Biol. & Med. **36**:535-540 (May) 1937.

Type II Infections.—Two epidemiological studies involving type II pneumococci are reported. In one [8] an epidemic was traced through healthy carriers from one winter to the next, when a new outbreak occurred centering about these carriers. In none of the carriers did pneumonia develop, but apparently they transmitted the infection to susceptible persons, who then contracted the disease. A specific vaccine used prophylactically seemed to check the spread.

The other report [9] concerns the development of type II pneumonia in 9 persons after an epidemic of infection of the respiratory tract in a camp. Nineteen per cent of the members of the camp were found to be carriers of this pneumococcus. Fifteen weeks later carriers of type II pneumococci were still present. No cases of pneumonia occurred in a similar camp in a different county in which a similar epidemic of infection of the respiratory tract occurred. These studies emphasize the importance of carriers in the transmission of pneumonia and what advances may be made in the understanding and control of epidemics when infectious diseases are regarded from an etiologic point of view.

Type III Infections.—A new mode of attack on type III infection is suggested by observations from two laboratories. It is a well known fact that most strains of type III pneumococci are avirulent for rabbits. Enders and Shaffer [10] attempted to discover the characteristics of certain strains of type III pneumococci on which depend survival or destruction of the organisms when they are injected into the rabbit. They subjected pneumococci of numerous strains to a temperature of 41 C. and found that the majority failed to grow. This suggested a possible relationship to the avirulence of type III pneumococci for rabbits, since the temperature of these animals was found to rise even higher than 41 C. after intravenous injection. After further trial they found that strains of pneumococci which grew at 41 C. were the only ones which were virulent for rabbits. Their work suggests that the rise in temperature following inoculation may be the most important factor in the natural resistance of the rabbit to certain strains of pneumococci. Further experiments by these investigators showed that not all "thermoresistant" strains are virulent. Other factors also exist,

8. Smillie, W. G.: A Study of an Outbreak of Type II Pneumococcus Pneumonia in the Veterans' Administration Hospital at Bedford, Massachusetts, Am. J. Hyg. **24**:522-535 (Nov.) 1936.

9. Harris, A. H., and Ingraham, H. S.: A Study of the Carrier Condition Associated with Type II Pneumonia in a Camp of the Civilian Conservation Corps, J. Clin. Investigation **16**:41-48 (Jan.) 1937.

10. Enders, J. F., and Shaffer, M. F.: Studies on Natural Immunity to Pneumococcus Type III, J. Exper. Med. **64**:7-18 (July) 1936. Enders, J. F.; Wu, C. J., and Shaffer, M. F.: Studies on Natural Immunity to Pneumococcus Type III, ibid. **64**:425-438 (Sept.) 1936.

such as the size of the capsule and the ease with which it is destroyed by humoral influences. Similar results, though derived from a different mode of attack, are reported by Rich and McKee.[11] They found that within twenty-four hours after injection of type III pneumococci rabbits become highly resistant to a second injection of similar organisms. Since this interval is too short to account for the development of specific immunity, the authors conclude that the fever which developed shortly after the first injection prevented growth of type III pneumococci, which cannot grow at similar high temperature in vitro. Under these conditions the cocci gradually lose their capsules and become subject to phagocytosis, or they may die without being taken up by cells. Phagocytosis in itself does not appear to be important. The results of both of these studies suggest the use of fever therapy in the treatment of human beings with infections due to type III pneumococci.

Experiments with antipneumococcus serum obtained from rabbits are being made with regard to the treatment of type III pneumonia. The subject is discussed in a subsequent paragraph.

Several studies have been made concerning the effectiveness of sulfanilamide in prolonging and saving the lives of mice[12] and rats[13] experimentally infected with type III pneumococci. Sulfanilamide was administered also to 13 patients[14] with type III pneumonia, 9 of whom recovered, in contrast with 10 patients who were not given the drug, 8 of whom died. The results are suggestive, but until a much larger series has been studied the clinical value of the drug cannot be appraised. The small number of cases should not give rise to false hopes and indiscriminate use of the drug to the exclusion of known and proved methods.

Type V Infections.—Finland and Tilghman[15] found that in 26 per cent of cases pneumonia caused by the type V pneumococcus was atypical clinically, in contrast with 4 per cent of those caused by the serologically related type II pneumococcus. There were also more

11. Rich, A. R., and McKee, C. M.: The Mechanism of a Hitherto Unexplained Form of Native Immunity to the Type III Pneumococcus, Bull. Johns Hopkins Hosp. **59**:171-207 (Sept.) 1936.

12. Rosenthal, S. M.: Studies in Chemotherapy: Chemotherapy of Experimental Pneumococcus Infections, Pub. Health Rep. **52**:48-53 (Jan. 8) 1937.

13. Gross, P., and Cooper, F. B.: Efficacy of *p*-Aminobenzenesulfonamide in Experimental Type III Pneumococcus Pneumonia of Rats, Proc. Soc. Exper. Biol. & Med. **36**:225-227 (March) 1937.

14. Heintzelman, J. H. L.; Hadley, P. B., and Mellon, R. R.: The Use of *p*-Aminobenzenesulphonamide in Type III Pneumococcus Pneumonia, Am. J. M. Sc. **193**:759-763 (June) 1937.

15. Finland, M., and Tilghman, R. C.: Clinical and Immunologic Observation in Cases of Pneumococcus Type V Pneumonia Treated with Specific Antibody, New England J. Med. **215**:1211-1221 (Dec. 24) 1936.

purulent complications in the cases of type V pneumonia than in those of pneumonia caused by the type II pneumococcus. They report the results obtained in 26 cases of type V pneumonia with specific antiserum, which was found to be a useful agent when given in adequate amounts early in the disease. The mortality rate in a series of 197 cases in which serum was not given was about 45 per cent, as compared with 15 per cent in 26 cases in which serum was given. Bullowa and Wilcox [16] report similar favorable results.

Barnes and Wight [17] raise the important academic question of the possible spontaneous transformation of type V into type II pneumococci.

Type VII Infections.—A study [18] of 160 cases of pneumonia caused by the type VII pneumococcus was made. The type VII pneumococcus also was encountered in numerous conditions other than pneumonia, as for example in meningitis, otitis media, peritonitis and various infections of the upper respiratory tract. In most of the cases the pneumonia was of the lobar form, but in about 20 per cent it was atypical. In 63 per cent of the cases pneumonia was preceded by some other infection of the respiratory tract. In only 22 per cent of the cases did the disease terminate favorably before the sixth day. In a series of 30 cases in which serum was given, the disease ended before the sixth day in 84 per cent of the cases in which recovery was obtained. The mortality rate in 130 cases in which serum was not given was 38 per cent, as compared with 10 per cent in 30 cases in which serum was given. Doses of from 80,000 to 100,000 units appeared to be adequate in cases of uncomplicated pneumonia. Twice the amount is advocated when bacteremia exists.

Type XIV Infections.—In a paper by Moor and Brown [19] one reads the amazing report that pneumococci were found in the urine of 30 per cent of 329 persons with infection of the genito-urinary tract; moreover, all of the 27 cultures which were "typed" showed type XIV pneumococci. These findings are so different from the reports of all previous observers that an immediate checking of the results is impera-

16. Bullowa, J. G. M., and Wilcox, C.: Therapeutic Serum of Pneumococcus Type V (Cooper) Pneumonia, J. Clin. Investigation **15**:711-715 (Nov.) 1936.

17. Barnes, L. A., and Wight, E. C.: Spontaneous Transformation of Pneumococcus Type V to Type II, J. Bact. **32**:557-566 (Nov.) 1936.

18. Finland, M.; Ruegsegger, J. M.; Dowling, H. F., and Tilghman, R. C.: Infections with Pneumococcus Type VII, Am. J. M. Sc. **193**:48-59 (Jan.) 1937. Finland, M.; Tilghman, R. C.; Ruegsegger, J. M., and Dowling, H. F.: Clinical and Immunological Observations, ibid. **193**:59-81 (Jan.) 1937

19. Moor, H. D., and Brown, I. D.: The Occurrence of Diplococcus Pneumoniae in Infections of the Urinary Tract, J. A. M. A. **108**:1594-1596 (May 8) 1937; abstr., J. Bact. **33**:73-74 (Jan.) 1937.

tive. It would be of interest to learn whether the type XIV pneumococcus is especially fitted to produce disease of the urinary tract, in a manner similar to that of the type II pneumococcus, which appears at times to have a special predilection for the endocardium.

Pneumonia in Infants and Children.—Bullowa and Greenbaum [20] studied pneumonia in 539 children, the majority of whom were under 6 years of age. Among infants under 2 years of age, type XIV pneumococci caused 18 per cent of the cases; type VI, 13 per cent; type XIX, 7 per cent, and type I, only 5 per cent. In patients over 2 years of age type I infections were dominant (24 per cent), with type XIV next in importance (13 per cent). Pneumococci of types V, VI, IV, III and VII were next in order of frequency. Pneumococcic pneumonia is three times as fatal in children less than 2 years old as in older children. Pneumonia which assumes the atypical or bronchial form is twice as fatal as the lobar form, regardless of the type of the pneumococcus.

Nemir and her associates [21] studied 1,033 cases of pneumonia in children and found that in 42 per cent the condition was associated with pneumococci of types I, VI and XIV. The type I pneumococcus was rarely found in infants under 2 years of age, while type XIX almost always occurred in children of this age. Type XIX and type VI occurred most often in those who did not have pneumonia, in contrast with type I and type XIV, which were rarely obtained from this group. Type I and type V pneumococci produced empyema in 39 per cent of the cases in which this complication developed. The highest death rate occurred among infants under 2 with atypical pneumonia or bronchopneumonia and in those with streptococcic and staphylococcic pneumonia. The mortality rate for patients with bronchopneumonia was 50 per cent, and that for patients with the lobar form was only 5 per cent. Specific serum therapy was most effective against infections caused by pneumococci of types I, XIV, V and VII.

Endemic Pneumonia.—Bullowa and Wilcox [22] made a survey of 4,048 cases of pneumonia noted during a seven year period to determine the incidence of various types of pneumococci involved. Similar surveys were made by Gundel several years ago. There were distinct differences from year to year and from month to month. It was noted,

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20. Bullowa, J. G. M., and Greenbaum, E.: Pneumococcic Pneumonia in Infants and in Children, Am. J. Dis. Child. **53**:22-31 (Jan.) 1937.

21. Nemir, R. L.; Andrews, E. T., and Vinograd, J.: Pneumonia in Infants and in Children, Am. J. Dis. Child. **51**:1277-1295 (June) 1936.

22. Bullowa, J. G. M., and Wilcox, C.: Endemic Pneumonia: Pneumococcic Types and Their Variations in Incidence and Mortality for Adults and Children, Arch. Int. Med. **59**:394-407 (March) 1937.

for example, that when the number of cases of type I pneumonia increased, the number of cases of type II pneumonia decreased. Type III and type VIII infections were more prevalent during the last two years than in the five preceding ones. Type V infection was prevalent in 1930; the incidence diminished and then increased to a new high level in 1934. Type VIII infections were prevalent all through the pneumonia season of 1934 to 1935, type I infections in January and February and type V pneumonia in April and May.

Finland [23] summarizes his studies of 3,682 cases in which the type of pneumonia was determined. The reader is referred to this paper for a statistical analysis and tabulation of many important features in regard to types of pneumococci.

Antipneumococcus Serum.—It appears that a distinct advance has been made by the substitution of rabbit serum for horse serum in the treatment of pneumonia. Goodner, Horsfall and Bauer [24] found considerable difference in the size, solubility and degree of specificity of the antibodies of serum from these species of animals. Some advantages of rabbit serum are as follows: 1. The potency is greater, as indicated by higher protection conferred on mice. 2. The smallness of the antibody permits greater diffusion of the serum. Immune bodies after intravenous injection have been demonstrated in empyema fluid. 3. The cost of preparing rabbit serum is less than that of preparing horse serum. 4. Unconcentrated rabbit serum is approximately as potent as concentrated horse serum. Methods are being developed for the refinement and concentration of rabbit serum. The results of the treatment of patients with antipneumococcus rabbit serum have been encouraging. Because of the small size of the protein molecule it is hoped that rabbit serum is more penetrative of serous membranes than horse serum and that it will favorably influence empyema, meningitis and other focal complications. Preliminary studies give encouragement, at least as far as empyema is concerned. Twenty-two patients were treated with rabbit serum, with no deaths from pneumonia.[25] In several cases the patient had an infected pleural exudate, which disappeared without thoracotomy—a notable fact. In my own experience the therapeutic response to rabbit serum has been favorable in pneu-

23. Finland, M.: The Significance of Specific Pneumococcus Types in Disease, Including Types IV to XXXII (Cooper), Ann. Int. Med. **10**:1531-1543 (April) 1937.

24. Goodner, K.; Horsfall, F. L., and Bauer, J. H.: Ultrafiltration of Type I Antipneumococcal Sera, Proc. Soc. Exper. Biol. & Med. **34**:617-619 (June) 1936.

25. Horsfall, F. L.; Goodner, K; MacLeod, C. M., and Harris, A. H.: Type Specific Antipneumococcus Rabbit Serum, Science **84**:579-581 (Dec. 25) 1936; Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia, J. A. M. A. **108**:1483-1490 (May 1) 1937.

monia caused by pneumococci of types III, IV, V, VII and XIV, but immediate or delayed reactions frequently occurred, indicating that further work must be done in refining the serum.

One company manufacturing biologic products has purchased 7,000 rabbits for making antipneumococcus serum and will probably place antiserums for all thirty-two types of pneumococci on the market next winter.

A study [26] is reported in which it is shown that the intravenous injection of serum is the method of choice, since a greater and more constant concentration is attained and the effects appear more rapidly and persist longer than when serum is given by the intramuscular or the subcutaneous route. Untoward reactions to initial injections were less frequent when serum was injected intramuscularly, which may be of practical importance in treating patients who are sensitive to serum.

Felton [27] marshals evidence to prove that pneumococcus antibodies found in horse serum are of protein nature. Chow and Wu [28] arrived at similar conclusions by isolating "immunologically pure antibody." They suggest the possibility of preparing potent antiserums for certain types of infection heretofore resistant to specific therapy, especially for type III pneumonia. By ultracentrifugation Wyckoff [29] succeeded in precipitating and concentrating immune bodies of type I antipneumococcus serum. The protein molecules found in the bottom layers had definite and constant physical characteristics. Protein molecules of similar nature were found in antiserum prepared with other types of pneumococci but not in normal horse serum. This precipitable globulin is perhaps made or freed in excess during the process of immunization. It was also found that the protein content was not increased in antipneumococcus serum containing both type I and type II antibodies, which indicates that a single globulin molecule can exhibit the characteristics of more than one antibody.

Miscellaneous.—In an epidemiological study Tilghman and Finland [30] present thirty-three groups of multiple cases of pneumococcic

26. Tilghman, R. C., and Finland, M.: The Availability of Specific Pneumococcus Antibody After Intravenous, Intramuscular and Subcutaneous Injection, J. Immunol. **31**:239-255 (Sept.) 1936.

27. Felton, L.: Pneumococcus Antibodies—What Are They? Science **79**:277-278 (March 23) 1934.

28. Chow, B. F., and Wu, H.: Isolation of Immunologically Pure Antibody, Science **84**:314 (Oct. 2) 1936.

29. Wyckoff, R. W. G.: The Ultracentrifugal Concentration of Pneumococcic Antibodies, Science **84**:291-293 (Sept. 25) 1936.

30. Tilghman, R. C., and Finland, M.: Pneumococcic Infections in Families, J. Clin. Investigation **15**:493-499 (Sept.) 1936. Finland, M., and Tilghman, R. C.: Bacteriological and Immunologic Studies in Families with Pneumococcic Infections, ibid. **15**:501-509 (Sept.) 1936.

infection apparently contracted directly from patients with the same type of infection. Most of the infections involved type I and type II pneumococci. In some instances the contracted infection appeared as lobar pneumonia; in others, as empyema, meningitis, otitis media or bronchopneumonia. A high incidence of carriers was noted in families in which various members had the infection. Serologic studies showed that homologous type-specific antibodies may appear in the blood of healthy contact carriers. Killian [31] believes that a hereditary familial disposition of susceptibility to pneumonia is present. This may be so, but one wonders if the examples of family infection which he cites are not simply the result of infections due to contact with carriers. A report [32] of experiments and observations in support of the value of artificial pneumothorax in the treatment of pneumonia has been published.

Numbers of cases of staphylococcic pneumonia, especially in children, are reported [33] which confirm my view in regarding this infection as a disease entity. Streptococcic septicemia [34] was discovered in 8 cases of pneumococcic pneumonia as a late complication or sequela. A review [35] of the literature and a study of pneumonia caused by Friedländer's bacillus was made. The records of 32 patients were studied, mostly persons in late middle life. The onset of pneumonia was usually abrupt, and the course was without any special clinical characteristics, except that the sputum, which was usually a thick mixture of mucus and blood, brick red and homogeneous, contained a predominance of capsulated gram-negative bacilli. Only one type of Friedländer's bacillus was isolated, namely, type A of Julianelle. Septicemia was present in 19 of 27 cases. There was a tendency to absolute or relative leukopenia. In about half the cases typical signs of consolidation were absent. Gross abscess formation was the most frequent complication; empyema and meningitis were less common. Specific antiserum was tested therapeutically, and no beneficial effect was noted.

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31. Killian, H.: Zur Frage der Disposition zur Pneumokokkenerkrankungen der Lunge, Klin. Wchnschr. **15**:1469-1471 (Oct. 10) 1936.

32. Kaltreider, N. L.; Hyde, H. V., and Fray, W. W.: Pulmonary Capacity in Lobar Pneumonia, with Special Reference to Collapse Therapy, Arch. Int. Med. **59**:408-431 (March) 1937.

33. Troisier, J.; Bariéty, M., and Brocard, H.: La staphylococcie pleuropulmonaire primitive, Ann. de méd. **39**:189-210 (Feb.) 1936. MacGregor, A. R.: Staphylococcal Pneumonia, Arch. Dis. Childhood **11**:195-205 (Aug.) 1936. Conklin, C. B.: Sporadic Outbreak of Neonatal Pneumonia, M. Ann. District of Columbia **5**:264-269 (Sept.) 1936.

34. Solomon, S., and Curphey, T. J.: Streptococcic Septicemia Complicating Pneumococcic Lobar Pneumonia, J. A. M. A. **108**:187-193 (Jan. 16) 1937.

35. Solomon, S.: Primary Friedländer Pneumonia, J. A. M. A. **108**:937-947 (March 20) 1937.

Thirty-one of the 32 patients died. Collins [36] reports a case of pneumonia due to Friedländer's bacillus and calls attention to the existence of chronic pulmonary disease caused by this organism which may easily be mistaken for tuberculosis unless the causative organism is identified.

INFLUENZA

A number of studies have confirmed and extended the highly important work on the etiology of influenza. In further investigation of the theory that the epidemic of swine influenza in 1918 was caused by the same virus which caused influenza in human beings at the same time, Shope [37] measured the neutralizing antibodies of the serum of persons of different ages. He showed that the serum of many adults who survived the pandemic of 1918 contained antibodies which neutralized the virus recently obtained from swine, whereas the serum from children born after 1918 did not. The results suggest that the virus in swine has persisted as such and that young persons who were not in contact with the virus of the pandemic therefore do not have neutralizing bodies in their serum. The same author [38] reviews the subject in a monograph. Francis and Magill [39] demonstrated protective antibodies for a strain of human influenza virus in about half of the persons over 1 year of age who were tested. A much higher percentage of serums of persons recently convalescent from influenza showed completely protective effects when tested on mice into which virus was injected. Virus neutralization tests were found to be accurate in determining early influenzal infection.[40] Human and swine viruses contain certain antigenic components in common. The same investigators [41] confirmed Elkele's work and succeeded in infecting pigs with virus derived from human beings. The disease caused by the human virus was less severe than that which followed experimental infection with swine virus in these animals, which indicates that the two strains

36. Collins, L. H.: Chronic Pulmonary Infection Due to the Friedländer Bacillus, Arch. Int. Med. **58**:235-249 (Aug.) 1936.

37. Shope, R. E.: The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages, J. Exper. Med. **63**:669-684 (May) 1936.

38. Shope, R. E.: Influenza of Swine and Man, Medicine **15**:453-487 (Dec.) 1936.

39. Francis, T., and Magill, T. P.: The Incidence of Neutralizing Antibodies for Human Influenza Virus in the Serum of Human Individuals of Different Ages, J. Exper. Med. **63**:655-668 (May) 1936.

40. Francis, T., and Shope, R. E.: Neutralization Tests with Sera of Convalescent or Immunized Animals and the Viruses of Swine and Human Influenza, J. Exper. Med. **63**:645-653 (May) 1936.

41. Shope, R. E., and Francis, T.: The Susceptibility of Swine to the Virus of Human Influenza, J. Exper. Med. **64**: 791-801 (Nov.) 1936.

are similar but not identical. Serial passage of human virus through swine did not enhance its virulence or change it immunologically. Further studies indicated some antigenic differences between certain strains derived from human sources which were previously thought to be identical.[42]

Practical application of the advances in knowledge has recently been made. Stokes and his associates [43] vaccinated about 250 persons in a large colony before an epidemic of influenza broke out which affected about 25 per cent of the group. Vaccine was made from virus obtained from both swine and human sources and grown in tissue culture, and from a 10 per cent emulsion of infected mouse lung in physiologic solution of sodium chloride. The emulsion was filtered and injected intramuscularly in doses of 0.5, 1 and 1 cc., respectively, at weekly intervals. The results of the vaccinations were as follows: In 12.5 per cent of 550 unvaccinated persons febrile infections developed; a similar percentage of those vaccinated with swine virus became ill, but in only 2.7 per cent of those vaccinated with human strains of virus did febrile disease develop. In all three groups the vaccine had no influence on the development of afebrile symptoms regarded as those of the common cold.

Stokes noted that persons who possessed virus-neutralizing bodies in their serum were still susceptible to the disease. It appears that as in other diseases, notably poliomyelitis, resistance to infection and neutralizing properties of the serum are associated but not always parallel. Similar observations were made by English investigators,[44] who also claim that the complement fixation test provides a possible method for differentiating immune from susceptible persons. By means of the test a high antibody titer was generally found in convalescent serum.

Two Russian investigators [45] sprayed cultures of Pfeiffer's bacillus (Haemophilus influenzae) into the respiratory tracts of 110 volunteers.

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42. Magill, T. P., and Francis, T.: Antigenic Differences in Strains of Human Influenza Virus, Proc. Soc. Exper. Biol. & Med. **35**:463-466 (Dec.) 1936. Francis, T.: Epidemiological Studies in Influenza, Am. J. Pub. Health **27**:211-225 (March) 1937.

43. Stokes, J.; Chenoweth, A. D.; Waltz, A. D.; Gladen, R. G., and Shaw, D.: Results of Immunization by Means of Active Virus of Human Influenza, J. Clin. Investigation **16**:237-243 (March) 1937.

44. Hoyle, L., and Fairbrother, R. W.: Isolation of the Influenza Virus and the Relation of Antibodies to Immunity, Brit. M. J. **2**:655-657 (March 27) 1937.

45. Smorodintseff, A. A.; Drobyshevskaya, A. I.; Ostrovskaya, S. M., and Shishkina, O. I.: Clinical and Laboratory Investigation on Volunteers Infected with Pfeiffer's Bacillus, Lancet **2**:1381-1383 (Dec. 12) 1936. Smorodintseff, A. A.; Drobyshevskaya, A. I., and Shishkina, A. O.: On Etiology of the 1936 Influenza Epidemic in Leningrad, ibid. **2**:1383-1385 (Dec. 12) 1936.

All the subjects became ill within from four to six hours but fortunately recovered in a day or two. The symptoms did not resemble those of grip or influenza, and leukocytosis was present in all. Contagion did not occur. The results proved the pathogenicity of Pfeiffer's bacillus, but the disease caused thereby did not resemble influenza. The same investigators isolated a filtrable virus from patients with influenza which was identical with the strains of the virus isolated in England.

Brightman and Trask [46] show how difficult it is to differentiate influenza from the common cold on a clinical basis. They believe it possible to make a definite diagnosis of influenza by producing symptoms in ferrets inoculated intranasally with nasopharyngeal secretions from the patients. Ferrets do not become ill when inoculated with secretion from normal persons or from those suffering from the common cold. The strain of influenza virus they isolated was immunologically similar to strains isolated by others from widely scattered sources.

Interesting observations made by Wells and Brown on the recovery of the virus of influenza from the air will be discussed in a later paragraph.

STREPTOCOCCIC INFECTIONS

Chemotherapy.—A great deal of attention has been focused on recent developments in chemotherapy. Interest has centered especially on the enthusiastic support given to the use of sulfanilamide and related substances.[47] The substances were introduced by Domagk in 1935 and tested clinically by French investigators and by Colebrook and his co-workers.[48] The papers of Colebrook [49] indicate the bene-

46. Brightman, I. J., and Trask, J. D.: Recovery of a Filtrable Virus from Children with Influenza: I. Epidemiologic and Clinical Observations, Am. J. Dis. Child. **52**:67-77 (July) 1936. Brightman, I. J.: Recovery of Filtrable Virus from Children with Influenza: Experimental Disease in Ferrets, ibid. **52**:78-91 (July) 1936.

47. Sulfanilamide and Related Compounds, report of the Council on Pharmacy and Chemistry, J. A. M. A. **108**:1888-1890 (May 29) 1937.

48. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250-253 (Feb. 15) 1935. Tréfouël J.; Tréfouël, J.; Nitti, F., and Bovet, D.: Activité du p-aminophénylsulfamide sur les infections streptococciques expérimentales de la souris et du lapin, Compt. rend. Soc. de biol. **120**:756-758, 1935. Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by *p*-Aminobenzenesulphonamide and Related Substances, Lancet **1**:1286-1290 (June 6) 1936.

49. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections, and of Experimental Infection in Mice, with Prontosil, Lancet **1**:1278-1286 (June 6) 1936; Treatment with Prontosil of Puerperal Infections Due to Haemolytic Streptococci, ibid. **2**:1319-1322 (Dec. 5) 1936. Colebrook, L.; Buttle, G. A. H., and O'Meara, R. A. Q.: The Mode of Action of *p*-Aminobenzenesulphonamide and Prontosil in Hemolytic Streptococcal Infections, ibid. **2**:1323-1326 (Dec. 5)

ficial effect of these substances in puerperal infections due to hemolytic streptococci. Striking results were obtained in 64 cases, in 12 of which bacteremia existed before treatment was started. The drug protected mice against experimental infection with this organism but had less effect against infection with meningococci and none against infection with pneumococci or staphylococci. Recovery has been reported in several cases of hemolytic streptococcic meningitis after chemotherapy.[50]

References to other papers on the subject published in European journals are given in a paper by Long and Bliss,[51] who confirmed many of the observations and add numerous data of their own. They found that the chemical exerted greater bacteriostatic action on certain strains of hemolytic streptococci than on others. The therapeutic effects were said to be remarkable. They report a series of 19 cases of infection with hemolytic streptococci in which favorable results were apparently due to the drug, but they cautiously add that the results noted may have been due to chance. Nevertheless, the careful clinical use of the compounds is warranted in the treatment of infections due to Streptococcus haemolyticus. In a later paper [52] they report a series of 74 cases, with only 4 deaths. Marshall [53] has found that the absorption of the drug from the intestinal tract is nearly complete in four hours. The drug is excreted in the urine when an equilibrium between intake and output is established after two or three days of treatment. The drug appears also in the spinal fluid after oral administration. Fortunately, sulfanilamide has several desirable qualities: It is of low toxicity, it is easily administered and absorbed, it is not too expensive, it seems to be more effective in vivo than in vitro and it seems to be more effective against virulent strains than against avirulent ones. Untoward

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1936. Foulis, M. A., and Barr, J. B.: Prontosil Album in Puerperal Sepsis, Brit. M. J. **1**:445-446 (Feb. 27) 1937. Mellon, R. R.; Gross, P., and Cooper, F. B.: Experimental Studies with Sulfanilamide and with Prontosil, J. A. M. A. **108**:1858-1861 (May 29) 1937.

50. Anderson, E. D.: Hemolytic Streptococcus Meningitis, J. A. M. A. **108**: 1591-1592 (May 8) 1937. Weinberg, M. H.; Mellon, R. R., and Shinn, L. E.: Two Cases of Streptococcic Meningitis Treated Successfully with Sulfanilamide and Prontosil, ibid. **108**:1948-1951 (June 5) 1937. Schwentker, F. F.; Clason, F. P.; Morgan, W. A.; Lindsay, J. W., and Long, P. H.: The Use of Para-Amino-Benzene-Sulphonamide or Its Derivatives in the Treatment of Beta Haemolytic Streptococcal Meningitis, Bull. Johns Hopkins Hosp. **60**:297-306 (April) 1937.

51. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives, J. A. M. A. **108**:32-37 (Jan. 2) 1937.

52. Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives, Arch. Surg. **34**:351-359 (Feb.) 1937.

53. Marshall, R. K.; Kendall, E., and Cutting, W. C.: Para-Amino-Benzene-Sulfonamide (Prontylin), J. A. M. A. **108**:953-957 (March 20) 1937.

effects noted are the development of acidosis,[54] anemia,[54a] jaundice, sulfhemoglobinemia and slight hematuria. Two deaths have been recorded, one [55] during administration of the drug and the other [56] as a result of sulfhemoglobinemia several days afterward. The presence of the benzene ring must be considered in regard to its possible effect on the granulocytes of the blood.

The mechanism of the effectiveness of sulfanilamide is unknown. Apparently hemolytic streptococci are not destroyed by the drug or by compounds formed from it. Bliss and Long,[57] however, suggest that reduced prontosil [58] is bacteriostatic, indicating the probable importance of the process of reduction. The frequency of acidosis in patients treated with this drug suggests the possibility that this factor is important in the antibacterial effect of the drug in vivo. It is presumed that the capsule of the organism is injured, that toxin formation is inhibited or that the reticulo-endothelial system is specifically activated, none of which theories is as yet proved.

The drug apparently has been received with the usual amount of overenthusiasm attendant on the introduction of any new remedy. Even Domagk has expressed his surprise over its widespread use. In the next few years one may anticipate a flood of papers on the subject describing the effects of the drug in a great variety of infections, but at present it appears to be of value only for infections caused by hemolytic streptococci and only against certain strains of this organism and possibly against meningococci and gonococci. Reports have already appeared of its use in infections caused by typhoid bacilli, in undulant fever and in gas gangrene. One must be exceedingly wary of early favorable reports which, although apparently convincing, make one mindful of the failure and disappointments with ethylhydro-

54. Southworth, H.: Acidosis Associated with Administration of Para-Amino-Benzene-Sulfonamide (Prontylin), Proc. Soc. Exper. Biol. & Med. **36**:58-61 (Feb.) 1937.

54a. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, J. A. M. A. **109**:12-16 (July 3) 1937.

55. Sommer, F.: Ein Zwischenfall nach intravenösen Prontosil-Injektion, Med. Klin. **32**:1076-1077 (Aug. 7) 1936.

56. Frost, L. D. B.: Sulphæmoglobinæmia Following Antistreptococcal Chemotherapy, Lancet **1**:510 (Feb. 27) 1937.

57. Bliss, E. A., and Long, P.: The Activation of "Prontosil Solution" in Vitro by Reduction with Cystine Hydrochloride, Bull. Johns Hopkins Hosp. **60**:149-153 (Feb.) 1937.

58. The term prontosil has been used for a number of related substances. Bliss and Long used the disodium salt of 4'-sulphanidophenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3,6-disulphonic acid.

cupreine, mercurochrome, acriflavine and other substances once so enthusiastically received. It is hoped that physicians will be critical in testing sulfanilamide and use it only for diseases against which controlled investigation has shown it to be of value, namely, infections caused by hemolytic streptococci.

Bacteriology.—Tillett [59] observed that serum obtained from patients during acute infections of various types has a bactericidal effect on hemolytic streptococci. Serum of the same patients soon after recovery or marked improvement no longer had this effect. Different strains of streptococci differed somewhat in susceptibility to the bactericidal effects. He noted a close parallelism between the bactericidal activity of the serum and the temperature level of the patient when the serum was taken, but he could not ascertain whether the fever or certain unknown factors inherent in febrile disease were responsible for the effect. The agglutinins or other measurable factors were apparently not involved. The bactericidal effect of the serum was inactivated by heat, and no effect was obtained when the test was made under anaerobic conditions.

It is difficult to correlate these results in vitro with those sometimes noted clinically. For example, it has long been believed that certain infections, like influenza, render the body especially favorable for the growth of hemolytic streptococci. Occasionally the organisms invade the blood of patients ill with pneumococcic pneumonia,[34] but more often they become invasive some time after the crisis. Serum is bactericidal for other organisms as well.[60]

In studying fibrinolysis, heretofore believed to be a property peculiar to the hemolytic streptococcus, Neter and Witebsky [61] found that Streptococcus viridans, Bacillus lactis-aerogenes, Friedländer's bacillus and the pneumococcus were also able to produce fibrinolysis if grown in broth containing 2 per cent dextrose. The hemolytic streptococcus was the only one of the group tested which produced fibrinolysis in mediums of low sugar content. In another paper [62] the authors report

59. Tillett, W. S.: The Bactericidal Action of Human Serum on Hemolytic Streptococci: Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, J. Exper. Med. **65**:147-162 (Jan.) 1937; Bactericidal Action of Human Serum on Hemolytic Streptococci: Factors Which Influence Phenomenon in Vitro, ibid. **65**:163-176 (Jan.) 1937.

60. Gordon, J., and Hoyle, L.: The Bactericidal Action of Serum Against Meningococcus, Gonococcus and Micrococcus Catarrhalis, J. Path. & Bact. **43**:537-544 (Nov.) 1936.

61. Neter, E., and Witebsky, E.: Fibrinolytic Activity of Hemolytic Streptococci and Other Microörganisms, Proc. Soc. Exper. Biol. & Med. **34**:549-552 (May) 1936.

62. Witebsky, E., and Neter, E.: Properties of Different Fibrinolysins Produced by Streptococci, Proc. Soc. Exper. Biol. & Med. **34**:858-863 (June) 1936.

the production of an anticoagulant by hemolytic streptococci grown in 2 per cent dextrose broth. Dart [63] confirmed their observation but is unable to attach any clinical significance as yet to the development of the anticoagulant.

In discussing the clinical significance of fibrinolysis Waaler [64] states that although the highest resistance to it is found in the blood after infections with hemolytic streptococci, resistance may occur also after pneumococcic pneumonia. In regard to rheumatic fever and rheumatoid arthritis, he doubts whether the antifibrinolytic quality of the serum justifies the assumption of a significant association between hemolytic streptococci and chronic arthritis.

Clinical Investigations.—Important epidemiological studies were made by English investigators [65] which demonstrated the value of accurate classification of bacteria. In one hospital during a period of three and one-half years, fourteen outbreaks of infections due to hemolytic streptococci were traced. The outbreaks usually occurred in the winter and were followed from patient to patient by the method for serologic classification devised by Griffith. Only by this method could the extent of spread of a specific bacterium be appreciated. When a certain type of streptococcic infection flared up, the infections in various persons were all due to the same type. The organisms were apparently disseminated by droplet infection and transmitted from patient to patient or through the agency of carriers to other patients. The clinical manifestations in different patients infected with the same type of organism varied greatly. In some there developed pharyngitis, otitis media or mastoiditis; in others, adenitis, erysipelas, scarlet fever, bronchopneumonia or septicemia. Operations on the nose and throat seemed to render patients more susceptible. In regard to the latter point, van der Hoeden [66] also points out the importance of local trauma in predisposing to infection. He cites several cases of subacute bacterial endocarditis occurring after dental extraction, paratyphoid fever after cholecystectomy, infection with Bacillus proteus after operation and fever following catheterization.

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63. Dart, E. E.: Streptococcus Anticoagulant, Proc. Soc. Exper. Biol. & Med. **35**:285-286 (Nov.) 1936.

64. Waaler, E.: Development of Antifibrinolytic Properties in Blood of Patients with Rheumatic Fever, Chronic Infective Arthritis and Bacterial Endocarditis, J. Clin. Investigation **16**:145-153 (Jan.) 1937.

65. Okell, C. C., and Elliott, S. D.: Cross-Infection with Hemolytic Streptococci in Otorhinological Wards, Lancet **2**:836-842 (Oct. 10) 1936. Brown, W. A., and Allison, V. D.: Infection of Air of Scarlet-Fever Wards with Streptococcus Pyogenes, J. Hyg. **37**:1-14 (Jan.) 1937.

66. van der Hoeden, J.: Bacteremia and Bacterial Localization, Nederl. tijdschr. v. geneesk. **81**:337-340 (Jan. 23) 1937.

Gottlieb [67] studied 30 cases of recurrence of scarlet fever which occurred between the twentieth and the thirtieth day after the first attack. The most likely explanation of the recurrence, he believes, is reinfection with a different type of streptococcus. His impression was supported by finding different types of streptococci in different patients with scarlet fever. Brody and Smith [68] made a careful pathologic study of scarlet fever and reviewed the literature on the subject. They found the pathologic changes in scarlet fever to be of a single type. The lesions were located primarily in blood vessels, with secondary infiltration into the adjacent interstitial tissues. Streptococci were rarely present in the lesions, which seemed to be due more to the action of circulating toxin. Hemolytic streptococci were, however, recovered in the majority of cases in postmortem cultures of blood and from visceral organs.

Pollock [69] analyzed 42 cases of streptococcic peritonitis. The infection was usually preceded by pharyngitis and became manifest with early abdominal distention, pain and tenderness. Definite diagnosis was made by abdominal puncture. The mortality rate was 80 per cent. Treatment is unsatisfactory. A case of endocarditis [70] and 2 cases of meningitis caused by enterococci are reported.[71]

A rather surprising paper [72] has been published dealing with the treatment of subacute bacterial endocarditis by splenectomy. The authors describe 4 cases, in 2 of which the diagnosis was doubtful. Splenectomy was performed, and all 4 patients died, 3 within three months and 1 in nine months; yet the authors believe that "life was unquestionably prolonged" by the operation. No necropsy report is given. They support their idea that splenectomy may be of value in sepsis with the doubtful hypothesis that the manufacture of toxins in secondary foci, such as the spleen, may be a chief cause of death. No one has as yet demonstrated a toxin in the infection in question.

67. Gottlieb, E.: So-Called Recurrence of Scarlet Fever, Ugesk. f. læger **98:** 1054-1058 (Oct. 29) 1936.

68. Brody, H., and Smith, L. W.: The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections, Am. J. Path. **12:**373-392 (May) 1936.

69. Pollock, L. H.: Primary Streptococcic Peritonitis, Arch. Surg. **33:**714-732 (Oct.) 1936.

70. Waaler, E.: Bacterial Endocarditis Caused by Hemolytic Fecal Streptococci (Enterococci), Acta med. Scandinav. **91:**121-159 (Jan. 20) 1937.

71. Lang, F. J.; Lode, A., and Schmuttermayer, F.: Ueber Enterokokken-Infectionen im Zentralnervensystem, Wien. klin. Wchnschr. **50:**29-35 (Jan. 8) 1937.

72. Riesman, D.; Kolmer, J. A., and Polowe, D.: Splenectomy in the Treatment of Subacute Bacterial Endocarditis, Am. J. M. Sc. **192:**475-483 (Oct.) 1936.

Furthermore, one is tempted to inquire about the importance of other secondary foci or of the primary focus itself, as discussed last year by Hamman and Rienhoff.[73] It seems that there is but little, if anything, to support the suggestion of splenectomy for septicemia due to any organism.

Muether and Kinsella[74] succeeded in producing endocarditis and septicemia in dogs. They first injured the valves of the heart surgically and then fed the animals a culture of Str. viridans obtained from a patient with subacute bacterial endocarditis. Five of the 12 dogs studied died. Necropsy showed bacterial endocarditis with vegetations.

Coburn and Moore[75] studied the relationship between Str. haemolyticus and erythema nodosum. By intracutaneous injection of the nucleoprotein derived from hemolytic streptococci they caused a local inflammatory reaction in 12 patients with erythema nodosum. In 6 patients recrudescences developed in previously affected areas shortly after the inflammatory reaction was noted. Spink[76] also studied the problem. In his opinion the lesions of erythema nodosum resembled histologically those produced by the injection of streptococci and broth filtrates of these organisms. A similar lesion was produced by the injection of tuberculin. He believes that erythema nodosum is a nonspecific inflammatory reaction of the skin to a variety of bacterial, toxic and chemical agents.

Dental Infection.—A valuable contribution to the bacteriology of the apexes of the teeth was made by the Dental Study Unit at Yale Medical School and is reported by Burket.[77] After a thorough review of the literature, in which great diversity of findings and opinions was noted, they made a careful study of the correlation of the bacteriologic, roentgenographic, gross anatomic and necropsy observations made on the teeth of patients. The meticulous care used in making the study enhances the value of the work. They found, as have others before, that organisms could be isolated from about 50 per cent of

73. Hamman, L., and Rienhoff, W. F., cited by Reimann, H. A.: Infectious Diseases: Review of the Current Literature, Arch. Int. Med. **58**:329-370 (Aug.) 1936.

74. Muether, R. O., and Kinsella, R. A.: Bacterial Endocarditis Following the Ingestion of Bacteria, J. Clin. Investigation **15**:449 (July) 1936.

75. Coburn, A. F., and Moore, L. V.: Experimental Induction of Erythema Nodosum, J. Clin. Investigation **15**:509-511 (Sept.) 1936.

76. Spink, W. W.: Pathogenesis of Erythema Nodosum, with Special Reference to Tuberculosis, Streptococcic Infection and Rheumatic Fever, Arch. Int. Med. **59**:65-82 (Jan.) 1937.

77. Burket, L. W.: Studies of the Apices of Teeth, Yale J. Biol. & Med. **9**:271-286 (Jan.); 348-358 (March) 1937.

the 419 periapical areas cultured. Streptococci, especially those of the viridans type, were present in 89 per cent of teeth, with positive results of culture. Staphylococci were next in order of frequency. Growth was obtained from 30 per cent of teeth without roentgenographic evidence of rarefaction at the root, from 76 per cent of those with a small periapical area lucent to roentgen rays and from 60 per cent of those with a large lucent area. Classified according to gross anatomic changes, organisms were isolated from 43 per cent of clinically normal teeth, from 38 per cent of carious teeth and from 72 per cent of "dead" teeth. The highest percentage of pure cultures was obtained from teeth with no periapical roentgenographic changes.

This report should be carefully studied by those who still attach undue importance to teeth as foci of infection, especially to roots which are so often erroneously regarded as "abscessed" simply because of apical lucency. It is obviously impossible to learn whether or not a root is "infected" by means of roentgen shadows alone. All rarefied areas are certainly not abscesses or the result of abscesses. It is urgently desired that this study group continue their investigation to determine the pathologic significance of teeth regarded as "infected" on such weak evidence.

RHEUMATIC FEVER

Several studies have dealt with the unsettled problem of the relation of hemolytic streptococci to rheumatic fever. Two English observers [78] emphasized the constitutional factors especially pertaining to abnormal capillary circulation. Persons of this type when exposed to cold and damp are more apt to have arthritis than normal persons. Infection, they believe, is the most important factor in predisposing patients to arthritis, and the hemolytic streptococcus is the most frequently incriminated organism. Keefer and Spink,[79] however, point out the contradictory fact that rheumatic fever was not noted to follow in any of 1,400 cases of erysipelas which they reviewed. Other studies, they claim, also fail to mention erysipelas as a prelude to rheumatic fever, whereas certain infections with hemolytic streptococci commonly precede it. They found the strains of streptococci isolated from patients with erysipelas to be no different from those causing other types of infection. Edström [80] observed several cases of rheumatic fever which followed trauma to a single joint, further adding to the obser-

78. Goldie, W., and Griffiths, G. J.: Aetiological Relation of the Streptococcus Haemolyticus to the "Rheumatic" Diseases, Brit. M. J. **2**:755-757 (Oct. 17) 1936.

79. Keefer, C. S., and Spink, W. W.: Studies of Hemolytic Streptococcal Infection, J. Clin. Investigation **16**:155-159 (Jan.) 1937.

80. Edström, G.: Mechanisches Trauma und nachfolgende Febris rheumatica, Acta med. Scandinav. **88**:342-353, 1936.

vations of Bland and Jones mentioned in last year's review.[81] Swift informs me that sulfanilamide had no beneficial effect on acute rheumatic fever.

Rinehart and his associates[82] found the vitamin C content of the blood in cases of rheumatic fever and rheumatoid arthritis to be uniformly reduced. The low levels may be raised by giving vitamin C. They could not ascertain whether the low level was due to inadequate intake, anorexia, digestive disorder or the disease itself.

Coburn and Moore[83] advance further evidence to illustrate the independence of chorea and rheumatic fever. They agree with other authors mentioned in the review[81] last year that the physiologic background prerequisite to the development of chorea may be prepared by a variety of abnormal conditions, of which the rheumatic state may be one. They found that in three fourths of the cases of chorea studied the condition was independent of rheumatic fever. Bourne[84] describes a case in which he regards chorea as due to acute rheumatic meningitis. Signs of meningitis developed during an attack of rheumatic fever. The spinal fluid was sterile and contained 78 leukocytes per cubic millimeter.

Wolffe and Brim[85] describe cases of rheumatic fever in children characterized by recurrent abdominal cramps. The problem of rheumatic involvement of the appendix is considered by others.[86]

Massel, Mote and Jones[87] injected 2 or 3 cc. of serum from patients with rheumatic fever subcutaneously into the patients' own tissue. A control group of normal persons and patients with chorea were similarly studied. Typical subcutaneous nodules developed in

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81. Reimann, H. A.: Infectious Diseases: Review of the Current Literature, Arch. Int. Med. **58**:329-370 (Aug.) 1936.

82. Rinehart, J. F.; Greenberg, L. D., and Baker, F.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **35**:347-350 (Nov.) 1936. Rinehart, J. F.; Greenberg, L. D., and Christie, A. V.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever, ibid. **35**:350-353 (Nov.) 1936.

83. Coburn, A. F., and Moore, L. V.: The Independence of Chorea and Rheumatic Activity, Am. J. M. Sc. **193**:1-4 (Jan.) 1937.

84. Bourne, G.: Acute Rheumatic Meningitis, Brit. M. J. **2**:1017-1018 (Nov. 21) 1936.

85. Wolffe, J. B., and Brim, C. J.: Abdominal Syndrome of Rheumatic Disease in Childhood, Am. J. Dis. Child. **52**:296-303 (Aug.) 1936.

86. Martin, A. T., and Ellenberg, S. L.: Rheumatic Involvement of the Appendix, J. Pediat. **9**:234-239 (Aug.) 1936.

87. Massel, B. F.; Mote, J. R., and Jones, T. D.: The Artificial Induction of Subcutaneous Nodules in Patients with Rheumatic Fever, J. Clin. Investigation **16**:125-128 (Jan.) 1937.

90 per cent of the patients with rheumatic fever who had received injections of their own serum, in 14 per cent of those with clinical evidences of infection, in 14 per cent of patients with chorea and in 3 per cent of normal persons.

The subject of chronic arthritis and rheumatism is reviewed in a comprehensive manner elsewhere [88] and need not be dealt with here.

STAPHYLOCOCCIC INFECTIONS

Numerous studies have been made of the treatment of infections caused by staphylococci. Clinical reports [89] on osteomyelitis stress the importance of the toxins elaborated by the organisms and of the use of immune serum in treatment. Since staphylococcus toxoid raises the titer of immune bodies in man, staphylococcus antitoxin may be of value in treatment. Immunotransfusion from a person convalescent from staphylococcic infection whose blood contains antitoxin is said to be of value. Another report [90] also emphasizes the toxemic symptoms of osteomyelitis. The authors state that commercial antitoxins neutralize in vivo the toxins of heterologous strains of staphylococci. They treated 16 patients with prompt drainage and multiple blood transfusions, 8 of whom recovered, in contrast with 11 recoveries among 13 patients treated with staphylococcus antitoxin. Buchman,[91] on the other hand, is not enthusiastic about the effects of toxoid in osteomyelitis. Among his patients who had been treated the magnitude of the titer of immune bodies gave no indication as to the progress of the disease for better or for worse. He attributes the disappointing results observed to the possibility that in the type of infection dealt with antitoxic immunity was not as important as the establishment of resistance to invasiveness, which toxoid does not provide. Dolman's favorable conclusions, Buchman claims, deal with generalities and impressions without adequate control and are insufficient to warrant enthusiasm. A good bibliography of the subject accompanies this paper. It is obvious that knowledge of staphylococcic infection is as yet too meager to permit one to speak with any certainty of specific treatment.

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88. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, T. P.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1935, Ann. Int. Med. **10**:754-909 (Dec.) 1936. This is a review of 530 papers.

89. Stookey, P. F.; Scarpellino, L. A., and Weaver, J. B.: Immunology of Osteomyelitis, Arch. Surg. **32**:494-505 (March) 1936.

90. Joyner, A. L., and Smith, D. T.: Acute Staphylococcus Osteomyelitis, Surg., Gynec. & Obst. **63**:1-6 (July) 1936.

91. Buchman, J.: The Use of Staphylococcus Toxoid in the Treatment of Chronic Osteomyelitis, J. A. M. A. **108**:1151-1156 (April 3) 1937.

Fisher [92] demonstrated plasma coagulation and fibrinolytic properties of staphylococci. Twenty-six of the thirty-four strains tested clotted plasma. All of the thirty strains from human sources clotted plasma. The inactive strains were usually of the albus nonhemolytic type, which are usually saprophytic. A strain which does not clot plasma almost certainly lacks pathogenicity. Fisher was unable to cause intravascular clotting. In further studies fifteen of twenty-six strains were slowly fibrinolytic. The author suggests that the spread of staphylococcic infection in patients may be related to the ability of the organisms to dissolve clots.

Julianelle [93] introduces a simpler method for the differentiation of staphylococci. He found that most pathogenic, type A, strains ferment mannitol, while most nonpathogenic, type B, strains do not. The error of the method was within 5 per cent.

MENINGITIS

A number of papers dealing with meningococcic infection have been published. Branham,[94] in discussing the significance of types, states that certain changes are necessary in the classification of meningococci. Type I and type III meningococci, for example, have become so closely interrelated that for practical purposes differentiation no longer seems to be necessary. The type I to type III group has apparently become predominant in many parts of the world. Type II and type IV are entirely distinct from types I to III and from each other, so that it seems necessary to deal with three general types, namely, I to III, II and IV. Type II meningococci are found largely in carriers and seldom in persons with disease, except in the cases of relatively mild or chronic septicemia. On the other hand, meningococcic endocarditis in nearly all cases has been due to organisms of the type I to type III group.

There is still difference of opinion as to whether or not type specific serum is effective only for the homologous type of organism. As Branham further points out, confusion has arisen in regard to the classification of meningococci according to type on an immunologic basis. During twenty years of observation certain strains have definitely changed their antigenic pattern. For example, a certain known strain of type I organism has apparently changed so that it now conforms

92. Fisher, A. M.: The Plasma-Coagulating Properties of Staphylococcus, Bull. Johns Hopkins Hosp. **59**:393-414 (Dec.) 1936; The Fibrinolytic Properties of Staphylococci, ibid. **59**:415-426 (Dec.) 1936.

93. Julianelle, L. A.: Determination of Staphylococcal Types by Fermentation of Mannite, Proc. Soc. Exper. Biol. & Med. **36**:117-119 (March) 1937.

94. Branham, S. E.: The Significance of Serologic Types Among Meningococci, J. A. M. A. **108**:692-696 (Feb. 27) 1937.

with the characteristics of type III. In considering epidemiological problems it is important that a world-wide type standard be established.

Alexander [95] tested the prognostic value of the precipitin ring test. Of 22 patients for whom the test gave positive results in ten minutes, 77 per cent died, in contrast with 4 per cent of the 47 patients for whom the test gave negative results. Branham states that the ring test can be performed at the bedside to determine the type of meningococcus and the selection of the proper type-specific therapeutic serum.

Hoyne [96] emphasizes the importance of regarding meningeal involvement as part of a systemic infection, the point being that intravenous serum therapy is of more value than intraspinal treatment. He treated all of his 66 patients intravenously; 31 received the new antitoxic serum and 35 the usual antimeningococcus serum. For those receiving antitoxic serum the fatality rate was 6.4 per cent, and the number of days spent in the hospital averaged 14.5; for those receiving antiserum the death rate was 14.2 per cent, and the number of days spent in the hospital averaged 15.3. Typing of meningococci was not considered. The death rate for the whole series of patients receiving intravenous therapy alone was 11.8 per cent, as compared with 50 per cent for the patients observed prior to 1934.

In discussing Hoyne's paper Kempf states that in a small series of his own patients the relative merits of antitoxin versus antimeningococcus serum reversed. Certain investigators in this field are unconvinced that the meningococcus actually produces a toxin.

Proom [97] found that sulfanilamide protected mice from meningococcic infection, but only if given immediately after the infection had developed. Schwentker, Gelman and Long [98] used sulfanilamide in the treatment of 10 patients with meningococcic meningitis. The results are said to be favorable and comparable to those which follow treatment with antiserum. Too few patients were treated to permit the drawing of definite conclusions regarding its use.

Reports of 2 cases of meningococcic myocarditis and a discussion of chronic meningococcic septicemia have been published.[99] Because

95. Alexander, H. E.: Prognostic Value of Precipitin Test in Meningococcus Meningitis, J. Clin. Investigation **16**:207-213 (March) 1937.

96. Hoyne, A. L.: Intravenous Treatment of Meningococcic Meningitis with Meningococcus Antitoxin, J. A. M. A. **107**:478-481 (Aug. 15) 1936.

97. Proom, H.: The Therapeutic Action of *p*-Aminobenzenesulphonamide in Meningococcal Infection of Mice, Lancet **1**:16-18 (Jan. 2) 1937.

98. Schwentker, F. F.; Gelman, S., and Long, P. H.: The Treatment of Meningococcus Meningitis with Sulfanilamide, J. A. M. A. **108**:1407-1408 (April 24) 1937.

99. Saphir, O.: Meningococcic Myocarditis, Am. J. Path. **12**:677-689 (Sept.) 1936. Appelbaum, E.: Chronic Meningococcus Septicemia, Am. J. M. Sc. **193**:96-108 (Jan.) 1937.

of certain biologic similarities of heat liability between meningococci and gonococci and the favorable effects reported by treating gonococcic infections with heat, it was obvious that the same treatment should be tested for meningococcic infections. In experiments thus far reported [100] most strains of meningococci were killed after eight hours at 41.5 C. (106.8 F.). On the basis of these findings 2 patients with chronic meningococcic infections were treated, and cure was said to have resulted from fever therapy. The authors do not recommend the use of fever therapy in acute meningococcic meningitis. Platou, McElmeel and Stoesser,[101] however, report the use of three sessions of fever therapy on alternate days for a child of 3½ years with acute meningococcic septicemia. Recovery followed.

Acute Lymphocytic Meningitis.—This type of meningitis is now established as a specific infectious disease caused by a filtrable virus. Viets and Warren [102] review the literature on the subject since 1934 and add several cases of their own, with careful histopathologic studies of a fatal case. Their cases illustrate three types of the disease—transient, prolonged and fatal. The clinical picture is similar in all three, differing only as to degree of severity. An epidemic involving 22 children in Cincinnati in the summer of 1935 is reported by Dummer and his associates.[103] The clinical characteristics were headache, vomiting and abdominal pain. Rigidity of the neck and the Kernig and the Brudzinski sign were frequently present. The cell count of the spinal fluid was usually elevated to 200 cells per cubic millimeter. Lymphocytes predominated, and the globulin content was increased in about half the patients. The fever lasted only a few days, and recovery was rapid and complete, with no sequela. There was no evidence of contagion, since the patients lived in widely separated areas. Charleux [103a] suggests that the disease may be acquired from dairy products.

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100. Bennett, A. E.; Person, J. P., and Simmons, E. E.: Treatment of Chronic Meningococcic Infections by Artificial Fever, Arch. Phys. Therapy **17**:743-749 (Dec.) 1936.

101. Platou, E. S.; McElmeel, E., and Stoesser, A. V.: Artificial Fever in the Treatment of Meningococcus Infection, Minnesota Med. **19**:781-782 (Dec.) 1936.

102. Viets, H. R., and Warren, S.: Acute Lymphocytic Meningitis, J. A. M. A. **108**:357-361 (Jan. 30) 1937.

103. Dummer, C. M.; Lyon, R. A., and Stevenson, F. E.: Benign Lymphocytic Meningitis (Aseptic Meningitis), J. A. M. A. **108**:633-636 (Feb. 20) 1937.

103a. Charleux, G.: La méningite bénigne des porchers, Presse méd. **45**:452-454 (March 24) 1937.

ENCEPHALITIS

Burdon, Thurston, Varney and Bronfenbrenner [104] followed Rosenow's technic carefully in studying the etiologic significance of streptococci in epidemic encephalitis. While the majority of cultures of material from the brain showed no growth and rarely streptococci, in agreement with the observations of others, culture of material from the nasopharynx showed a predominance of green-producing streptococci. No significant results were obtained with agglutination tests, however, nor could the authors confirm Rosenow's measurements of cataphoretic velocity. In a second study they could establish no biologic relationship between streptococci and the virus isolated from patients with the disease in St. Louis. No evidence was found to support the view that streptococci represent the primary etiologic agents of epidemic encephalitis. In spite of a great mass of evidence to the contrary,[105] Rosenow [106] seems oblivious to all criticism and continues to champion his views undaunted. He now has a "virus derived from streptococci" which produces first encephalitic and then poliomyelitic lesions in monkeys.

An epidemic of encephalitis involving 160 persons occurred in Pennsylvania in the summer of 1935.[107] It began in July and lasted until September. The infection appeared to be spread by droplet infection, for it was contagious and affected entire families in some cases. Children and young adults were chiefly involved. The incubation period varied from three to ten days. Headache, nausea, vomiting, photophobia, stiffness of the neck, backache, cramps, muscle pains, nervousness, insomnia and vertigo were common complaints. Physical signs were minimal. The Kernig sign was noted occasionally. Sore throat was almost always present. The cell count and the globulin content of the spinal fluid were increased even in cases of subclinical encephalitis. The disease was mild, as a rule, and few sequelae followed. Only 1 patient died. The use of convalescent serum seemed to be of value prophylactically and therapeutically.

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104. Burdon, K. L.; Thurston, E. W.; Varney, P. L., and Bronfenbrenner, J.: Etiologic Significance of Streptococci in Epidemic Encephalitis: Incidence of Streptococci in Cultures from Patients with Encephalitis in St. Louis and from Normal Controls, and Characteristics of Various Strains Isolated, Arch. Int. Med. **58**:285-308 (Aug.) 1936; Etiologic Significance of Streptococci in Epidemic Encephalitis: Experiments with Animals and Conclusions, ibid. **58**:469-494 (Sept.) 1936.

105. Rivers, T. M.: Viruses and Koch's Postulates, J. Bact. **33**:5-6 (Jan.) 1937.

106. Rosenow, E. C.: Further Studies on the Relationship of Streptococci to the Viruses of Encephalitis and Poliomyelitis, ibid. **33**:61-62 (Jan.) 1937.

107. Slesinger, H. A.: Acute Epidemic Encephalitis, Am. J. M. Sc. **192**:225-234 (Aug.) 1936.

POLIOMYELITIS

Nearly 11,000 cases of poliomyelitis were reported by the United States Public Health Service in 1935. An excellent survey of the problem of immunity in poliomyelitis has been published by Harmon and Harkins,[108] who critically review recent studies on the subject and point out certain peculiarities of the disease which have been baffling. For example, a specific virus-neutralizing substance is found more often in adults without a history of contact or infection than in persons convalescing from the disease. The importance of attempts to increase immune substances artificially is therefore questioned. Because of the present uncertainty of methods in current use, the authors still recommend the employment of convalescent serum and other specific serum therapy since no evidence, they claim, has shown that they are not of value. Schultz,[109] however, in a paper presented before the International Congress for Microbiology in London, states that enough is now known about the pathogenic and immunologic features of the disease to cast considerable doubt on the belief that it will ever be controlled by means of serums or vaccines.

Howitt [110] studied an outbreak of poliomyelitis in California and isolated a strain of virus which differed immunologically from other well known strains. She suggests the probability that various types of virus exist and produce diseases of clinically similar characteristics, which have come to be recognized as poliomyelitis.

Observation [111] was made of the effect of a preceding mild infection in producing resistance to poliomyelitis. Monkeys previously inoculated with the virus of dog distemper were inoculated with a strain of poliomyelitis which ordinarily killed them. The results were surprising, in that 66 per cent of the inoculated animals recovered. It is assumed that the effects of the preceding distemper in some way protected the monkeys against poliomyelitis. Opportunity was provided to test the value of trinitrophenol and alum nasal spray in preventing poliomyelitis during an epidemic in Alabama.[112] The disease developed

108. Harmon, P. H., and Harkins, H. N.: The Significance of Neutralizing Substances in Resistance and Recovery from Poliomyelitis, J. A. M. A. **107**:554-558 (Aug. 22) 1936.

109. Schultz, E. W.: Immunity and Prophylaxis in Poliomyelitis, J. A. M. A. **107**:2102-2104 (Dec. 26) 1936.

110. Howitt, B. F.: A Recently Isolated Strain of Poliomyelitis Virus, Science **85**:268-270 (March 12) 1937.

111. Dalldorf, G.; Douglass, M., and Robinson, H. E.: The Sparing Effect of Dog Distemper on Experimental Poliomyelitis, Science **85**:184-185 (Feb. 12) 1937.

112. Armstrong, C.: Experiences with Picric Acid-Alum Spray in Prevention of Poliomyelitis in Alabama, 1936, Am. J. Pub. Health **27**:103-112 (Feb.) 1937.

in a number of persons who had used the substance. The failure to protect suggested that the chemicals are not as effective and trustworthy in man as in animals.

Lucchesi [113] believes that many patients in the Philadelphia area who showed fever, headache, cervical rigidity, vomiting and lymphocytes in the spinal fluid without paralysis actually were suffering from poliomyelitis. Because of the absence of paralysis the disease was probably erroneously diagnosed as choriomeningitis or encephalitis. It is obvious that great care must be taken in differentiating infections of this nature from one another. Biologic methods of diagnosis, though intricate, must be used more frequently, since clinical data alone are insufficient.

TULAREMIA AND PLAGUE

Tularemia.—Foshay [114] reports further observations on the cutaneous reaction which occurs after the intradermal injection of specific antiserum into patients suffering from tularemia. All of the 450 patients showed a positive reaction, while normal persons showed no response. The reaction is erythematous-edematous in nature and becomes maximal in from fifteen to twenty minutes. The reaction was diagnostically positive for tularemia in some cases on the first day of illness and in 1 case twenty-two years after recovery. The degree of perfection claimed for this test is remarkable and sets it apart from most other biologic tests, which are much more frequently unreliable. Foshay believes that the reaction is due to the antigen-antibody union, which involves only the species-specific polysaccharide. The suggestion is made that a similar test might be of value in diagnosis and treatment by determining the specificity of other infections as well.

In another study the same author [115] found viable bacilli in certain patients long after there had apparently been full recovery from the initial infection. The observation illustrates the dictum that is true of many other infections, to wit, "once infected, always infected." The constant presence of organisms is a continuous source of danger, and exacerbations of disease flare up periodically when the delicate equilibrium between host and parasite is disturbed by various causes. The condition is exemplified in a patient who had intermittent symptoms and recurrent adenopathy for eight years. The persistence of Pasteurella tularensis in the body may explain the well known fact that agglutinins

113. Lucchesi, P. F.: Nonparalytic Poliomyelitis Versus Choriomeningitis, J. A. M. A. **108**:1494-1496 (May 1) 1937.

114. Foshay, L.: The Nature of the Bacterial-Specific Intradermal Antiserum Reaction, J. Infect. Dis. **59**:330-339 (Nov.-Dec.) 1936.

115. Foshay, L., and Mayer, O. B.: Viability of Bacterium Tularense in Human Tissues, J. A. M. A. **106**:2141-2143 (June 20) 1936.

for this organism persist for many years. Blackford and Smith [116] also report a case in which bacilli were still obtainable from a lesion twenty-one months after the primary infection. McGovern [117] describes a case in which the primary ulcer of tularemia appeared in the pharynx. The patient crushed infected ticks and probably introduced the infection into his mouth with his fingers.

A new and unexpected mode of transfer of tularemia is propounded by two Russian investigators.[118] An epidemic broke out among some field workers, especially those who drank water from a brook which was inhabited by water rats. Most of the patients had the "anginal" form of tularemia, while the rest showed the typhoid or oculoglandular form, which suggested that the infection was water borne and entered through the tonsils, the oral mucosa and the conjunctivae. All guinea-pigs inoculated with the water under suspicion died of tularemia. It is of interest to recall that a previous epidemic of tularemia in Russia was associated with rodents during a flood.

In Austria [119] and Czechoslovakia [119a] tularemia has been recognized for the first time and has again been regarded by some as a new disease. Among the 200 cases studied during the past year there were several of the newly recognized "anginal" form, with acute tonsillitis and swelling of the cervical lymph nodes. It seems strange that a disease with symptoms and signs as characteristic as those of tularemia should have been overlooked in a country as medically advanced as Austria; yet I agree with Pilot that the disease doubtlessly existed unrecognized for many years.

An epidemic of tularemia in Utah is reported on by Hillman and Morgan.[120] It involved 26 of a group of 170 men engaged in road work in hot weather. Many of the men worked without shirts or other covering above the waist and were bitten by horse-flies or deer-flies. In no instance did the disease develop in a fully clothed man. The incident again calls forcibly to mind the chain of events or factors necessary in epidemics, namely, the source of infection (sick rabbits were noted in the vicinity), the great agent of conveyance (probably

116. Blackford, S. D., and Smith, D. C.: Prolonged Virulence of Bacterium Tularense in Human Tissue, South. M. J. **29**:1062-1067 (Nov.) 1936.

117. McGovern, F. H.: Primary Tularemic Ulcers in the Pharynx, J. A. M. A. **107**:1629-1630 (Nov. 14) 1936.

118. Karpoff, S. P., and Antonoff, M. I.: Spread of Tularemia Through Water, as a New Factor in Its Epidemiology, J. Bact. **32**:243-259 (Sept.) 1936.

119. Tularemia in Austria, Foreign Letters, J. A. M. A. **108**:1813-1814 (May 22) 1937.

119a. Tomanek, E.: Tularemia in Czechoslovakia and Austria During 1936 and 1937, Am. J. Pub. Health **27**:443 (May) 1937.

120. Hillman, C. C., and Morgan, M. T.: Tularemia, J. A. M. A. **108**:538-540 (Feb. 13) 1937.

deer-flies) and the susceptible host. It also emphasizes the importance of prophylaxis in avoiding insect bites in areas where tularemia is endemic.

It is now a well known fact that tularemia often breaks out as an epizootic when certain animal populations are high. Sylvest [121] believes that tularemia may have been accountable for the great mortality rate among lemmings during their strange periodic migrations to the sea. Simultaneously an unusual disease in man was recognized for centuries in Norway. The descriptions of the disease, called lemming fever, as early as 1532 and 1633 coincided closely with that of tularemia.

Plague.—Meyer [122] discusses the controversy which has arisen over the relationship of "sylvatic" plague of wild rodents to the plague of the domestic rat, which is the usual source of the disease in human beings, although wild rodents apparently were responsible for the explosive outbreak in Manchuria in 1910 and in California in 1920. There is even uncertainty as to the choice of the term sylvatic or selvatic; the former seems to be preferable. There is reason to agree with Meyer that the variety of plague prevalent among rodents in the United States is different from that which caused the "black death." Type differentiation recognized for many other species of bacteria no doubt exists also among plague bacilli. According to recent reports of the United States Public Health Service, 2 cases of plague occurred in California, 1 case in Utah and 1 in Hawaii in 1936. Plague occurred in ground squirrels in California, Oregon, Montana and Idaho; in fleas from squirrels in Nevada and Washington, and in marmots and prairie dogs in Utah. Seventy-two species of rodents are known to suffer from plague. In this respect another similarity may be pointed out between the organism causing plague and its close relative Past. tularensis, which is also known to invade many species of animals and birds.

A comprehensive survey of plague has been published by Wu and his colleagues.[123]

UNDULANT FEVER

Hardy, Jordan and Borts [124] summarize the important advances in the knowledge of undulant fever. Undulant fever is really not one

121. Sylvest, E.: Tularemia—Disease of Lemmings, Ugesk. f. læger **98**:307-310 (April 9) 1936.

122. Meyer, K. F.: The Sylvatic Plague Committee, Am. J. Pub. Health **26**: 961-969 (Oct.) 1936.

123. Wu, L. T.; Chun, J. W. H.; Pollitzer, R., and Wu, C. Y.: Plague: A Manual for Medical and Public Health Workers, Shanghai, Weishungshu National Quarantine Service, 1936.

124. Hardy, A. V.; Jordan, C. F., and Borts, I. H.: Undulant Fever, J. A. M. A. **107**:559-563 (Aug. 22) 1936.

disease but a group of three closely related diseases caused, respectively, by the bovine, the porcine and the caprine strain of Brucella. Disease due to the bovine variety is most prevalent in regions where this variety is most widely distributed, for example, in the eastern part of the United States. Disease due to the porcine variety occurs more often in the middle western states, where hogs are more common. Brucella of the porcine variety was recovered in 70 per cent of cases in Iowa and in 60 per cent in Minnesota.[125] In the state of New York 93 per cent of isolated strains were of the bovine variety. The porcine variety is the more invasive and dangerous. It frequently gives rise to localized infections which are often suppurative, frequently involving the skeletal system. The recognition of these suppurative lesions as being caused by Brucella is one of the most important of recent contributions to clinical knowledge. Evans[126] reviews the history of undulant fever as derived from goats in the United States. The disease is believed to have existed in Texas for at least fifty years. Twelve cases were reported in 1911. Her own studies showed the prevalence of caprine strains in North Carolina and Kansas. Cattle were found to be frequently infected with the caprine variety, which is of significance, since infections caused by these organisms are usually severe.

The increasing number of cases reported (1,897 cases in 1935) is often believed to indicate a spread or an increase of undulant fever. It is far more likely, however, that it represents merely its more frequent recognition. Studies of the incidence of infection among cattle, as a matter of fact, show a surprisingly even distribution in all sections of the United States. It seems, then, that many more unrecognized or unreported cases exist among human beings. In regard to treatment, Hardy states that as yet no conclusive evidence as to the value of specific therapy has been obtained. A report[127] of the successful treatment of meningitis due to Brucella with immune serum from a convalescent patient has been published, but other workers[128] claim to have obtained good results, as have numerous observers previously, in 10 of 12 patients with the nonspecific therapy consisting of injection of typhoid vaccine.

125. Kabler, P., and MacLanahan, M.: A Differential Study of Forty Brucella Strains Isolated in Minnesota, J. Infect. Dis. **58**:293-298 (May-June) 1936.

126. Evans, A. C.: The Distribution of Brucella Melitensis Variety Melitensis in the United States, Pub. Health Rep. **52**:295-303 (March 12) 1937.

127. Poston, M. A., and Smith, D. T.: Successful Treatment of Brucella Meningitis with Immune Human Serum, New England J. Med. **215**:369-383 (Aug. 27) 1936.

128. Ervin, C. E.; Hunt, H. F., and Niles, J. S.: Foreign Protein Therapy, Am. J. M. Sc. **192**:234-241 (Aug.) 1936.

Prickman and Popp [129] treated 4 patients with the Simpson-Kettering hypertherm with apparent good results, although they are cautious in drawing conclusions, realizing that undulant fever is a disease characterized by natural remissions and exacerbations. In another unusual case [130] of undulant fever with degenerative myositis, fever therapy was apparently of benefit.

Keller and his associates [131] estimated the relative value of several diagnostic tests. The agglutination test was found to be most dependable for patients during the active stage of the disease but may often show negative results in those who have been infected previously. The intracutaneous test determines a state of allergy resulting from infection with Brucella and is useful in ascertaining the general incidence of infection in large groups of persons. The authors believe that the opsonocytophagic test gives the best information as to the status of immunity of the patient. It is possible, they state, to determine whether persons are susceptible, infected or immune by the use of the intracutaneous and the opsonocytophagic test together. From experience with complicated tests in other infections, one wonders whether or not the last statement is not somewhat too optimistic. Actual immunity or susceptibility is often unrelated to measurable factors in the test tube.

Among the many manifestations of undulant fever, encephalitis was recently discussed.[132] In the author's 4 cases, however, the diagnosis of undulant fever must be accepted with reservation, since it was based on only a positive cutaneous reaction and positive results of agglutination tests. Furthermore, the possibility of the occurrence of "nonspecific" encephalitis, common to many other infections, must be considered.

TUBERCULOSIS

Only a few of the numerous papers on tuberculosis published in the past year are selected for comment here. Miller and Rappaport [133] in a timely paper point out the difficulties inherent in interpreting the reaction to injected tuberculin. Many factors, both specific and non-

129. Prickman, L. E., and Popp, W. C.: Treatment of Brucellosis by Hyperpyrexia Induced by the Simpson-Kettering Hypertherm, Proc. Staff Meet., Mayo Clin. **11**:506-510 (Aug. 5) 1936.

130. O'Donoghue, A. F., and Scott, W.: Degenerative Myositis from Melitensis Infection, Nebraska M. J. **21**:462 (Dec.) 1936.

131. Keller, A. E.; Pharris, C., and Gaub, W. H.: Diagnosis of Undulant Fever, J. A. M. A. **107**:1369-1373 (Oct. 24) 1936.

132. McCullagh, E. P., and Clodfelter, H. M.: Encephalitis Due to Undulant Fever: Report of Four Cases, Ann. Int. Med. **10**:1508-1513 (April) 1937.

133. Miller, J. A., and Rappaport, I.: Resistance in Tuberculosis, J. A. M. A **107**:471-474 (Aug. 15) 1936.

specific, condition the response. The specific factors concern acquired, inherited and accumulated resistance, while the nonspecific factor may be thought of as constitutional in nature. Since there exists no means of distinguishing these various factors and since the reaction to tuberculin consists of merely an allergic response, one therefore cannot know which of the factors are concerned. Conclusions based on the test alone may therefore be misleading.

Gardner [134] believes that the lesions of silicosis and those of tuberculosis are histologically similar. For instance, both conditions give rise to a primary mononuclear cell reaction and produce epithelioid and giant cells; both cause exudation and necrosis, and in each calcification may occur. The tuberculin test, however, elicits a positive reaction only in the presence of tuberculous disease. Gardner casts doubt on the specificity of certain chemical fractions of the tubercle bacillus in causing given cellular reactions, as shown by others.

Kereszturi and Park [135] report observations made over eight years on BCG vaccine. They believe it to be free from danger. The death rate from tuberculosis was twice as high among unvaccinated children. Among control patients who showed a negative reaction to the Mantoux test the death rate was four times as high as among infants vaccinated with BCG. They suggest that BCG be used as a public health measure for the prevention of tuberculosis in those who have not yet become infected and who may later be exposed. This study and the following one add support to the opinion of those who do not regard a positive reaction to the tuberculin test as a liability, as discussed in last year's review.[81]

Increased inflammation after reinfection, Lurie [136] thinks, may play a rôle in immunity. I believe with him that the allergic reaction, with its outpouring of exudate, may tend to fix organisms early and prevent their spread. Vaccination with BCG afforded pronounced protection. Contrary to previous general opinion, the humoral factor of immunity is thought to be important in tuberculosis. While the fibrin barriers erected at the site of the allergic reaction may localize small doses of bacilli, when large doses are used the increased lymphatic flow may bring about increased rapidity of dissemination. Much depends, it seems, on the intensity of the reaction, on the size of the dose of infect-

134. Gardner, L. U.: Similarity of Lesions Produced by Silica and by Tubercle Bacillus, Am. J. Path. **13**:13-25 (Jan.) 1937.

135. Kereszturi, C., and Park, W. H.: Use of BCG Vaccine Against Tuberculosis in Children: Eight Years' Experience, Am. Rev. Tuberc. **34**:437-456 (Oct.) 1936.

136. Lurie, M.: On the Mechanism of Immunity in Tuberculosis, J. Exper. Med. **63**:923-946 (June) 1936.

ing organisms and on the general condition of the animal. I am not as convinced as Lurie is of the importance of rapidly mobilized mononuclear cells in destroying tubercle bacilli. No one has yet proved that phagocytosis per se is of great importance in infectious disease.

Bogen [137] kept guinea-pigs inoculated with tubercle bacilli at a high temperature (85 to 90 F.) for long periods to determine the effect of thermotherapy. The animals that were kept warm showed much less extensive tuberculosis after three months than did control animals. Bogen believes these results occurred because heated animals kept quieter, rested more and incidentally reduced the spread of infection to each other.

TYPHOID

In 1936 only 1 death from typhoid per hundred thousand life insurance policy holders was recorded,[138] as compared with 23 deaths twenty-five years ago. This infection has registered the largest percentage of decline of all causes of death in the given period; yet no satisfactory method of specific therapy has been achieved. The decline is apparently due entirely to preventive measures.

Attempts are still being made to develop specific antiserums. Two papers [139] dealing with the subject have been published, but the results are not encouraging. Similar unconvincing reports of cases in which serum was used appeared in a paper [140] dealing with "immunotransfusion." In most of the charts designed to illustrate the effectiveness of this form of therapy, the temperature seemed to be declining before the injection of blood.

Gannon [141] reports a case illustrating the persistence of typhoid bacilli in persons recovered from typhoid. Bacilli were isolated from an abscess of the sternum nearly six years after recovery from typhoid. In an experimental study [142] "typhoid leukocidin" from typhoid bacilli was found to reduce the number of neutrophilic granulocytes. Its

137. Bogen, E.: Thermotherapy in Experimental Tuberculosis, Proc. Soc. Exper. Biol. & Med. **36**:11-16 (Feb.) 1937.

138. Statist. Bull., Metropolitan Life Ins. Co. **18**:4 (Jan.) 1937.

139. Shwartzman, G.; Baehr, G., and Hollingsworth, W. Y.: Treatment of Typhoid with an Antitoxic Antityphoid Serum, Arch. Int. Med. **58**:799-811 (Nov.) 1936. Robertson, R. C., and Yu, H.: The Serum Treatment of Typhoid Fever, Brit. M. J. **2**:1138-1140 (Dec. 5) 1936.

140. Habel, K., and Crocker, W. J.: Treatment of Nineteen Cases of Typhoid Fever in Children, J. Pediat. **9**:149-166 (Aug.) 1936.

141. Gannon, J. A.: Typhoid Abscess About Lower End of Sternum, J. A. M. A. **105**:113 (July 13) 1935.

142. Dennis, E. W., and Senekjian, H.: Typhoid Leucocidin, Proc. Soc. Exper. Biol. & Med. **36**:61-63 (Feb.) 1937.

action was neutralized by immune globulin. The leukocidin was believed to be responsible for the leukopenia of typhoid.

Goodpasture [143] presents new light on the pathogenesis of typhoid. He points out that the primary site and the mechanism of invasion are still unknown. In 1 case studied at necropsy he observed small gram-negative intracellular bacilli in the cytoplasm of plasma cells of the lymphoid follicles of iliac and mesenteric lesions early in the course of the disease. He regards these as typhoid bacilli modified by existence within the cells. He believes, therefore, that the portal of entry is by way of these cells and also by way of the cytoplasm of the large macrophages in which the usual large form of typhoid bacilli are found. The plasma cells may serve as the focus of infection during the period of incubation and also throughout the entire course of the illness. It remains to be proved whether or not the bacillary inclusions are actually viable typhoid bacilli.

Salmonella Suipestifer (Hog-Cholera Bacillus) Infection.—Numerous observers have presented case reports of this infection. The bacillus was first erroneously associated with "hog cholera" years ago but has since been recognized as a human pathogen. It is a frequent cause of food poisoning but apparently may also reside in the human gastrointestinal tract as a commensal until a lowering of the resistance permits it to become invasive and cause disease. The infection often occurs secondary to other illness and during times of war, famine and exposure. The subject is reviewed by Harvey,[144] who adds data on 21 new cases. The majority of cases occur in children. The infection often resembles typhoid, so that an accurate diagnosis can be made only by isolating the bacillus from the blood and identifying it by means of special bacteriologic methods. Localization [145] in various parts of the body may occur, for instance, as pneumonia, arthritis, meningitis or endocarditis. The mortality rate among patients less than 25 years old was 19 per cent; for those over 25 it was 58 per cent.

Others [146] have reviewed the literature on meningitis caused by bacilli of the Salmonella group. For only 19 of the 34 cases reported

143. Goodpasture, E. W.: Concerning the Pathogenesis of Typhoid Fever, Am. J. Path. **13**:175-185 (March) 1937.

144. Harvey, A. M.: Salmonella Suipestifer Infection in Human Beings, Arch. Int. Med. **59**:118-135 (Jan.) 1937. Boycott, J., and McNee, J. W.: Human Infection with American Hog-Cholera Bacillus, Lancet **2**:741-742 (Sept. 26) 1936. Frank, T. J. F.: Salmonella Infections: Report of Sporadic Case of Bacillus Enteritidis (Gärtner) Septicemia, M. J. Australia **1**:457-463 (March 27) 1937.

145. Cohen, L.; Fink, H., and Gray, I.: Salmonella Suipestifer Bacteremia, with Pericarditis, Pneumonitis and Pleural Effusion, J. A. M. A. **107**:331-333 (Aug. 1) 1936.

146. Bahrenburg, J. H., and Ecker, E. E.: Meningitis Due to Organisms Belonging to the Salmonella Group, J. Infect. Dis. **60**:80-87 (Jan.-Feb.) 1937.

can positive diagnosis be accepted, since in many cases adequate identification was not made.

BACILLARY DYSENTERY

Felsen [147] made a follow-up study of 122 patients who had dysentery in an epidemic caused by Flexner bacilli in New Jersey in 1934. About one third of them had recurring diarrhea or bloody stools for a long time thereafter. In 10 per cent chronic ileitis or ulcerative colitis had developed by the end of the first year. In many it appeared that the original attack had merely subsided, never having cleared up completely. Bacilli were still recoverable from a small percentage of patients, but secondary infection of the bowel with enterococci and Bacillus coli was common. Felsen calls attention to the importance of recognizing atypical forms with appendicular involvement, distal ileitis and mesenteric lymphadenitis. He reports several cases of dysentery ushered in with symptoms of pneumonia. In a study [148] of dysentery in England, many patients infected with Sonne type did not have the typical symptom of bloody diarrhea. Ulcerative colitis was, however, noted as a sequela. The Shiga type of dysentery was almost never encountered. Bacillary dysentery has apparently been endemic since the fourteenth century. It is continuously renewed by returning tourists who bring back new strains.

Rothman [149] reviews the literature pertaining to dysentery bacillemia and adds a report of a case of his own. Frequently the clinical picture resembles that of typhoid. Diagnosis can be made only by cultivating the organism from the blood and identifying it. Dysentery bacteremia probably occurs more often than is ordinarily believed. Two cases of bacillemia are reported by Haynes.[150]

In a paper presented before the Harvard Tercentenary Conference in September 1936 Shiga [151] discusses the advances of knowledge of dysentery since his discovery of the causative organism thirty-eight

147. Felsen, J., and Gorenberg, H.: Chronic Dysentery, Distal Ileitis and Ulcerative Colitis, Am. J. M. Sc. **192**:553-556 (Oct.) 1936. Felsen, J.: Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Non-Specific Intestinal Granuloma, Ann. Int. Med. **10**:645-669 (Nov.) 1936; Pneumonic Type of Bacillary Dysentery, New York State J. Med. **37**:253-254 (Feb. 1) 1937.

148. Hurst, A. F., and Knott, F. A.: British Dysenteric Infections, Lancet **2**:1197-1201 (Nov. 21) 1936.

149. Rothman, P. E.: Dysentery Bacillemia, J. Pediat. **9**:167-172 (Aug.) 1936.

150. Haynes, E.: A Bacteriologic Study of Forty Cases of Dysentery in Infants and Children, J. Infect. Dis. **60**:251-256 (March-April) 1937.

151. Shiga, K.: The Trend of Prevention, Therapy and Epidemiology of Dysentery Since the Discovery of Its Causative Organism, New England J. Med. **215**:1205-1211 (Dec. 24) 1936.

years ago. He says that it appears most desirable at present to classify the organism into three types, as follows:

I. Bacillus dysenteriae (Shiga-Kruse)

II. Bacillus metadysenteriae (representative strains: Flexner, Strong, Y, Ohno and Schmitz)

III. Bacillus paradysenteriae (representative strains: Kruse-Sonne and Ohara-Mita)

Dysentery endotoxin, he claims, produces an antitoxin, but toxoid treatment has been unsuccessful. Antitoxic serum, however, gives good results, especially in cases of mild or moderately severe involvement. In cases of severe dysentery in which the toxin has acted on the peristaltic centers in the intestinal wall and paralysis has set in, antitoxin is of no value. A mild toxin stimulates peristalsis and causes diarrhea; strong toxin causes paralysis. Serum therapy is not effective in type II or type III infections. In Japan in recent years it seems that type I, or Shiga, strains have been replaced by type II or type III strains (see also the discussion of changes of type in the concluding paragraphs of this review).

Shiga states that 30 per cent of convalescent patients continue to excrete bacilli for months. About 9 per cent of familial contacts were found to be carriers. Seventy-five per cent of the patients were less than 10 years of age. He mentions the oral administration of vaccine but does not recommend it, because of its nonproved value. I believe Shiga's method of classification into three types as types I, II and III is an improvement, but I do not favor the prefixes meta- and para- in bacterial nomenclature.

Amebic Dysentery.—A complete report of the Chicago outbreak of amebic dysentery has been published by the United States Public Health Service.[152]

MISCELLANEOUS INFECTIONS

Tetanus.—In further work on tetanus Abel and his associates[153] studied the distribution and fate of toxin in the body. Toxin in excess of a lethal dose accumulates in the blood and lymph, and only a negligible amount is found in the tissue spaces. About 90 per cent can be recovered from the blood and lymph; the remainder is irremovably fixed to the tissue cells. Toxin which can be recovered from organs of an infected animal is only that which is contained in the blood or lymph.

152. Epidemic Amebic Dysentery: The Chicago Outbreak of 1933, Bulletin 166, National Institute of Health, United States Treasury Department, Public Health Service, 1936.

153. Abel, J. J.; Evans, E. A., and Hampil, B.: Researches on Tetanus, Bull. Johns Hopkins Hosp. **59**:307-391 (Nov.) 1936.

An important point in regard to therapy which has emerged from these valuable experiments is the fact that the time of death of infected animals is predetermined. Whether a moderate amount of toxin or a great excess is injected, the actual time of death is definitely determined in each case by the absolute amount which has been irretrievably fixed in the various organs of the body in the first few hours after the requisite threshold concentration in the tissue spaces has been attained. "The events of these early hours initiate the period of incubation, determine its duration, and are decisive for life and death." If this is actually the case in human beings, any hope resting on the present form of antitoxin therapy must be deferred.

Several observers [154] recently analyzed 642 cases of tetanus. Specific antitoxic treatment, they conclude, has accomplished relatively little in the way of saving of life. They believe sedatives constitute the most hopeful form of therapy.

Rickettsial Diseases.—Pinkerton [155] warns against inaccurate and unnecessarily complex classification of diseases of this group. He urges that classification be made on the basis of morphologic and histopathologic changes in infected tissues and on immunologic studies rather than on variations in the clinical picture in man and in animals. He presents in tabular form the differences between certain diseases caused by Rickettsia. In another paper,[156] methods for tissue culture for biologic study and classification of Rickettsiae are described.

Lewthwaite and Savoor [157] have published data to show the identity of "rural typhus" of Malaya and tsutsugamushi disease. They suggest that the former term be abandoned. "Urban typhus" of Malaya and Rocky Mountain spotted fever possess a minor degree of reciprocal cross-immunity, but their exact relationship is still undetermined.

Zinsser [158] states that although the mode of transmission of typhus fever is well known, sanitary measures alone are not sufficient to con-

154. Huntington, R. W.; Thompson, W. R., and Gordon, H. H.: The Treatment of Tetanus with Antitoxin, Ann. Surg. **105**:93-96 (Jan.) 1937.

155. Pinkerton, H.: Criteria for the Accurate Classification of the Rickettsial Diseases (Rickettsioses) and of Their Etiological Agents, Parasitology **28**:172-188 (March) 1936.

156. Pinkerton, H.: The Application of Tissue Culture to the Morphological and Biological Study and Classification of Rickettsiae, Arch. f. exper. Zellforsch. **18**:343-359, 1936.

157. Lewthwaite, R., and Savoor, S. R.: The Typhus Group of Diseases in Malaya: Relation of Rural Typhus to Tsutsugamushi Disease with Special Reference to Cross Immunity Tests, Brit. J. Exper. Path. **17**:448-460 (Dec.) 1936; Typhus Group of Diseases in Malaya: Relation of Tsutsugamushi Disease (Including Rural Typhus) to Urban Typhus, ibid. **17**:461-472 (Dec.) 1936.

158. Zinsser, H., and Macchiavello, A.: Further Studies on Typhus Fever, J. Exper. Med. **64**:673-687 (Nov.) 1936.

trol epidemics. He suggests mass vaccination with rickettsial cultures treated with solution of formaldehyde, which can now be made on a large scale. Attempts to produce immunity in guinea-pigs with serovaccination (mixtures of virulent defibrinated guinea-pig blood and convalescent serum) were successful.

Dengue.—Dengue, ordinarily regarded as an exotic disease, is as a matter of fact prevalent in the southern part of the United States. In 1934, for instance, 10,000 cases were recorded in Florida. Griffitts and Hanson[159] review the problem and bring out a number of interesting points. The disease in the United States is transmitted only by the Aedes Aegypti mosquito. To become infective the mosquito must secure blood from a patient in the first forty-eight hours of the initial fever. The mosquito is then noninfectious for about twelve days (extrinsic incubation period), but after this time it is infectious for the duration of its life. The intrinsic incubation period in man lasts for from four to ten days. When an epidemic breaks out, the disease is spread from person to person with great rapidity, second only to that of influenza. In Galveston, for example, about 60 per cent of the population suffered attacks in 1932. In Athens, Greece, 239,000 cases were reported in the 1928 epidemic. Warm wet weather favors the multiplication of the mosquitoes which spread the disease.

Allusion has been made to the similarity in the epidemiological characteristics of dengue and yellow fever and of the ever present danger of an outbreak of the latter disease if conditions become favorable.

Cheney[160] reports 20 cases of "dengue-like fever" in California. The disease frequently exhibited a course of biphasic fever. Identity with true dengue was not established.

Pleurodynia.—Two outbreaks of pleurodynia have been recognized for the first time in the middle western states.[161] The one observed in Ohio involved at least 282 persons. Many more, unreported, cases are presumed to have existed. The epidemic began in June, reached its height in August and disappeared in October. Children and young adults were chiefly affected. The contagiousness of the disease was indicated by its appearance in twenty-four groups of "contact cases." The disease, as in other epidemics reported previously, was characterized by severe pain in the region of the diaphragmatic attachment to the thorax.

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159. Griffitts, T. H. D., and Hanson, H.: Significance of an Epidemic of Dengue, J. A. M. A. **107**:1107-1110 (Oct. 3) 1936.

160. Cheney, G.: A Dengue-Like Fever, California & West. Med. **46**:8-11 (Jan.) 1937.

161. Welborn, M. B.: Epidemic Pleurodynia, Am. J. M. Sc. **191**:673-678 (May) 1936. Harder, F. K.: Epidemic Myalgia or Pleurodynia in Southwestern Ohio, ibid. **191**:678-685 (May) 1936.

Nerve Infections.—Davis [162] reports an unusual disease in 10 children. It was characterized by a segmental distribution of pain, often with hypesthesia and hyperalgesia, which followed other infections, particularly of the respiratory tract. He suggests that a neurotropic virus, probably activated by the preceding infection, attacked the posterior spinal nerve roots and their ganglions. The disease may be regarded as a form of herpes zoster, since vesiculation occurred in 2 cases. A review of the literature revealed other similar observations.

Another comparatively rare neurologic disease, acute infective polyneuritis, is discussed by Pinckney,[163] of England. The causative virus, it is claimed, has been isolated and passed through monkeys. The infection is classified into three types: one, afebrile, with painless peripheral neuritis with rapid onset; the second, with fever, peripheral polyneuritis, facial paralysis and slight general bulbar weakness; the third, with ascending polyneuritis and involvement of the muscles of respiration, simulating Landry's paralysis.

Yellow Fever.—Soper [164] sums up the knowledge recently gained about the epidemiology of yellow fever. A decade ago yellow fever was believed to have been exterminated in South America, only to crop up again and again in the subsequent years to the disillusionment of interested epidemiologists. The disease was found to be widespread after the introduction of the viscerotome [165] to obtain hepatic tissue without necropsy by which positive identification of yellow fever can be made by histologic examination. Furthermore, it soon became obvious that the mode of transmission of infection concerned other means beside the Aedes Aegypti mosquito, which formerly was believed to be solely responsible, since cases were noted in persons in regions where this mosquito was not present. This newly recognized form of the disease, called "jungle yellow fever," is endemic and permanent, in contrast with the mosquito-transmitted form, which flares up and dies out in scattered areas. The viruses of these infections are believed to be identical. The source of the disease is still unknown, although immunity tests reveal protective substances in the blood of opossums and monkeys, suggesting that these and other animals may serve as reservoirs of infection.

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162. Davis, J. H.: Segmental Neuralgia in Children Simulating Visceral Disease, J. A. M. A. **107**:1620-1625 (Nov. 14) 1936.

163. Pinckney, C.: Acute Infective Polyneuritis, Brit. M. J. **2**:333-335 (Aug. 15) 1936.

164. Soper, F. L.: The Newer Epidemiology of Yellow Fever, Am. J. Pub. Health **27**:1-14 (Jan.) 1937.

165. Rickard, E. R.: The Organization of the Viscerotome Service of the Brazilian Cooperative Yellow Fever Service, Am. J. Trop. Med. **17**:162-190 (March) 1937.

Leishmaniasis.—The search in the western hemisphere for diseases related to Old World kala-azar has continued since Darling's investigation in 1906. More recently De Monbreun isolated an organism from a patient with histoplasmosis in the southern part of the United States. He regards the organism as a fungus rather than a protozoan parasite. There is, however, still a question of the possible relationship of this organism to the Leishmania group.

In the course of investigation by the viscerotome service of the Rockefeller Foundation in Brazil for the detection of yellow fever, eighty-five specimens of liver containing Leishmania bodies were encountered by Penna. After this observation Chagas [166] made a study of the disease caused by these organisms and found it to correspond closely with typical kala-azar in regard to clinical course, laboratory tests and histologic lesions. The disease occurs throughout the northern and eastern parts of Brazil and in the Chaco territory of the Argentine. Fifty-three per cent of cases occurred in children less than 6 years of age. Antimony derivatives were of value in the treatment.

Several French investigators [167] have had success in diagnosing kala-azar by making sternal or tibial puncture rather than splenic puncture to obtain material for study. The former method, they say, is less dangerous and is especially useful in the case of infants.

Schistosomiasis.—Exotic diseases are easily missed by physicians not familiar with them. It is always important to bear them in mind in dealing with a person recently arrived from other portions of the world, especially in the case of certain infections, such as kala-azar and schistosomiasis, in which specific therapy may save the patient's life. A case of imported schistosomiasis was studied by Hoff.[168] The symptoms were those of cirrhosis of the liver with ascites and 50 per cent eosinophils. Therapy with antimony and potassium tartrate was apparently begun too late, for the patient died. A second patient, a carrier, was freed from parasites with a trivalent sodium antimony compound (fuadin).

Actinomycosis.—Physicians are likely to acquire certain mental associations in therapeutics which are difficult to alter. An example is the fungous infection-potassium iodide complex which arose on an empirical

166. Chagas, E.: Visceral Leishmaniasis in Brazil, Science **84**:397-398 (Oct. 30) 1936.

167. Lorando, N.: Sternal Puncture in Leishmaniasis, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:314-316 (March 8) 1937. Giraud, P., and Gaubert: Value of Bone Marrow Puncture for Diagnosis of Mediterranean Kala Azar, ibid. **53**:336-339 (March 15) 1937.

168. Hoff, A.: Schistosomiasis: Report of Two Cases, J. A. M. A. **107**:1375-1378 (Oct. 24) 1936.

basis years ago. To my knowledge the iodides have never been proved to be of specific value in fungous infections. Wangensteen [169] reviewed a number of cases of actinomycosis and says he was unable to note any benefit whatever from these salts. The effects of irradiation are also discussed without enthusiasm. The treatment of choice is the surgical removal of infected material, when possible, and the curettage and evacuation of dead tissue in the visceral forms. Thymol therapy has recently been recommended.[170]

Appendicitis.—Wangensteen and Bowers [171] briefly discuss the literature in regard to the etiology of appendicitis and add their own experimental observations. Obstruction and infection are the two most important causative factors experimentally in the dog. Obstruction was always followed by inflammation; obstruction of an appendix previously washed out was usually well tolerated, and infection without obstruction did not produce inflammation. Appendical concretions were the acutely obstructing agent in most instances of perforated appendix in man.

Rabies.—Webster and Clow [172] and Kanazawa [173] cultivated rabies virus in vitro. Tissue culture virus vaccine is safer than brain or spinal cord substance containing the virus, since the superfluous animal tissue may in itself cause paralysis or secondary infection. In another study [174] the presence of neutralizing antibodies in mice failed to guarantee the existence of immunity. A surprising observation was that vaccine containing no demonstrable living virus produced resistance. It is generally believed that the injection of dead filtrable virus does not confer immunity. Rabies virus may be an exception to the rule.

Vincent's Stomatitis.—Farrell and McNichols [175] made a critical study of the value of various forms of treatment of stomatitis that

169. Wangensteen, O. H.: The Rôle of Surgery in the Treatment of Actinomycosis, Ann. Surg. **104**:752-770 (Oct.) 1936.

170. Myers, H. B.: Thymol Therapy in Actinomycosis, J. A. M. A. **108**:1875 (May 29) 1937.

171. Wangensteen, O. H., and Bowers, W. F.: An Experimental Study of the Significance of the Obstructive Factor in the Genesis of Acute Appendicitis, Tr. West. S. A. **45**:195-252, 1935.

172. Webster, L. T., and Clow, A. D.: Propagation of Rabies Virus in Tissue Culture and Successful Use of Culture Virus as an Antirabic Vaccine, Science **84**:487-488 (Nov. 27) 1936.

173. Kanazawa, K.: In Vitro Culture of Rabies Virus, Jap. J. Exper. Med. **15**:17-28 (Feb.) 1937.

174. Webster, L. T.: Diagnostic and Immunological Tests of Rabies in Mice, Am. J. Pub. Health **26**:1207-1210 (Dec.) 1936.

175. Farrell, G. W., and McNichols, W. A.: Efficacy of Various Medicaments in the Treatment of Vincent's Stomatitis, J. A. M. A. **108**:630-633 (Feb. 20) 1937.

is believed by some to be caused by fusiform and spiral organisms. Neoarsphenamine, chromium trioxide, ultraviolet rays, aconite, iodine, chloroform, potassium arsenite, aniline dyes and other remedies were found to be without value. They observed the development of Vincent's disease in 6 patients under intensive treatment with neoarsphenamine for syphilis, an occurrence previously observed by others. The most effective method of treatment included oral hygienic measures, removal of mechanical irritation, abstinence from tobacco and avoidance of surgical treatment of the mouth. Solution of hydrogen peroxide U. S. P. favored the cure of the infection when used as a mouthwash.

Thrombo-Angiitis Obliterans.—Allen and Lauderdale [176] briefly review certain experiments designed to demonstrate the infectious nature of thrombo-angiitis obliterans. The results in general were inconclusive, yet the disease seems to be infectious in origin. The authors describe the case of a surgeon who six months previous to observation had amputated the toe of a man with the disease. During the operation the palmar surface of the surgeon's third finger was accidentally pierced by a spicule of bone. Although no local lesion was noted, a month later changes in color, consisting of cyanosis and pallor on exposure to cold, developed in the injured finger. Several weeks later similar changes occurred in other fingers of the same hand. The symptoms diminished somewhat but had not disappeared entirely. A diagnosis of thrombo-angiitis obliterans was made. The possibility of coincidental development of the disease was considered, but the local development of the condition after a definite history of injury with possibly infective material strongly suggested the infectious nature of the disease.

Bacteroides Funduliformis Infection.—Attention is called [177] to this unusual form of infection, which was observed in 6 cases. It occurs most often in patients with necrotic ulcerating carcinoma of the bowel. The organisms frequently invade the blood; hepatic abscesses were found in all fatal cases. The infection should be suspected when icterus appears in the type of patient mentioned. The authors also review the literature on the subject.

Toxoplasmosis.—Toxoplasma, a protozoan parasite of various mammals and birds, has been described in various parts of the world but has been almost unnoticed in North America. The organism, like certain viruses, grows only within living cells, but it has been cultivated

176. Allen, E. V., and Lauderdale, T. L.: Accidental Transmission of Thrombo-Angiitis Obliterans from Man to Man, Proc. Staff Meet., Mayo Clin. **11**:641-644 (Oct. 7) 1936.

177. Dixon, C. F., and Deuterman, J. L.: Postoperative Bacteroides Infection, J. A. M. A. **108**:181-185 (Jan. 16) 1937.

in vitro with chick embryo.[178] It is virulent for mice, guinea-pigs and rabbits; in monkeys it causes febrile, nonfatal disease. Some years ago Bland, in England, induced toxoplasmosis in rabbits into which had been injected blood from patients with infectious mononucleosis. It was uncertain whether the toxoplasma was the cause of the human disease or whether the organism was harbored in the rabbit as a commensal.

MISCELLANEOUS STUDIES

Air-Borne Infection.—Statement was made in a preceding paragraph of the remarkable decline in the incidence of typhoid, to which may be added other infections of the gastro-intestinal tract. This has largely been brought about by the control and prevention of contamination of food and drink. One might contrast this achievement with the unchanged incidence of infections known to be air borne, such as the common cold, influenza, pneumonia, meningitis and others, which together are responsible for 85 per cent of deaths from infectious disease. A reduction of these diseases might be anticipated should methods be developed to sterilize the air. The magnitude of such a problem is obvious. In two papers presented at the Harvard Tercentenary in August 1936, W. F. Wells and M. W. Wells[179] point out that under conditions of living in enclosed rooms persons are inhaling one another's nasopharyngeal flora as once they ingested each other's intestinal flora in food and water supplies. In ingenious experiments these investigators developed an apparatus to spray organisms into the air and another to centrifugate the air so as to concentrate bacteria and viruses contained therein for tests. They studied the length of time during which droplets of varying size containing bacteria remain suspended in the air and tested the viability of floating organisms. For example, H. influenzae died in one hour, whereas staphylococci, pneumococci, streptococci and diphtheria bacilli remained viable for several days. Organisms of the "intestinal group" seldom survived more than eight hours. The virus of influenza when sprayed into the air could be recovered up to an hour by centrifugation.

In tests to determine measures which may serve to sterilize air, ultraviolet irradiation with a quartz mercury vapor lamp was most effective. Air contaminated with known bacteria was passed at definite distances through ultraviolet rays. Organisms which divide in one plane, such as streptococci and pneumococci, were easily destroyed, but

178. Sabin, A. B., and Olitsky, P. K.: Toxoplasma and Obligate Intracellular Parasitism, Science **85**:336-338 (April 2) 1937.

179. Wells, W. F., and Brown, H. W.: Recovery of Influenza Virus Suspended in Air, Science **84**:68-69 (July 17) 1936. Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107**:1698-1703 (Nov. 21) 1936; Air-Borne Infection: Sanitary Control, ibid. **107**:1805-1809 (Nov. 28) 1936.

the outer layers of cocci which grow in clumps protected the inner ones from the rays. The virus of influenza was easily destroyed.

The importance of studies such as these can hardly be overestimated, since they suggest definite lines of attack on the spread of air-borne infectious diseases.

Mandelic Acid Therapy.—After so many disappointments in the field of chemotherapy for infections due to bacterial diseases, it is but natural to regard the introduction of any new substance with skepticism. It is surprising, therefore, that within a year or two two substances were proposed, sulfanilamide and mandelic acid, both of which appear to have real merit. Only further work can tell if either is as valuable as early reports indicate. Mandelic acid has been the subject of numerous published articles,[180] a few of which are referred to here. The development and use of the drug were based on the observations of Shohl and Janney, who demonstrated the importance of a low hydrogen ion concentration of the urine in combating infections due to colon bacilli, and of Clark and Helmholtz, who developed the ketogenic diet. After Fuller showed that betahydroxybutyric acid was an important factor of this treatment, Rosenheim, in England, suggested the use of mandelic acid, which produced a condition in the urine similar to that which resulted from the use of the unpleasant ketogenic diet.

Most of the papers thus far published on the subject are favorable to its use. It is emphasized, however, that before benefit can be expected therefrom, any existing obstructive lesions must be corrected and free drainage established. Thus far the effects obtained by the proper use of the mandelic acid and proper acidity of the urine are said to indicate the superiority of this drug to all other forms of medication of urinary infections. It is important, however, to establish the etiologic diagnosis in all cases before treatment, since the drug is apparently specific only for infections caused by colon bacilli. Little or no beneficial effect was obtained in infections due to Bacillus proteus, Bacillus pyocyaneus or the staphylococcus.

Antiseptics.—Nye [181] calls attention to the absurdity of the variety of antiseptics in common use at present, few of which have actual

180. Rosenheim, M. L.: Mandelic Acid in the Treatment of Urinary Infections, Lancet **2**:1083-1087 (Nov. 7) 1936. Helmholtz, H. F., and Osterberg, A. E.: Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, J. A. M. A. **107**:1794-1796 (Nov. 28) 1936. Carrol, G.;; Lewis, B., and Kappel, L.: Mandelic Acid as a Urinary Antiseptic, ibid. **107**:1796-1799 (Nov. 28) 1936. Cook, E. N., and Buchtel, H. A.: Mandelic Acid in the Treatment of Infections of the Urinary Tract, ibid. **107**:1799-1800 (Nov. 28) 1936. Dolan, L. P.: Experience with Ammonium Mandelate in Urinary Infections, ibid. **107**:1800-1805 (Nov. 28) 1936.

181. Nye, R. N.: The Relative in Vitro Activity of Certain Antiseptics in Aqueous Solution, J. A. M. A. **108**:280-287 (Jan. 23) 1937.

value. Tests were made in vitro for the purpose of measuring certain qualities that seemed most desirable in antiseptics used for the treatment of wounds, cuts, abrasions or irritations. Solutions containing iodine, mercury, chlorine and other chemicals were tested. Of all antiseptics studied, compound solution of iodine U. S. P. possessed more of the desirable qualities of effectiveness, with low cost, than any of the other antiseptics tested.

Lyophile Serum.—Mudd and his associates [182] report their studies on the preservation of serum by drying in vacuo. By means of this technic human serum (convalescent serum) can be collected at times of epidemics and preserved in the dry state for future use. When serum is desired for use, the dried porous mass can be redissolved in a volume of liquid smaller than the original one, which permits a fourfold concentration. In another paper [183] the results of clinical use of lyophile serums in various diseases is reported. The results compare favorably with those of other serums when used in the prophylaxis of scarlet fever, measles, mumps, whooping cough and German measles and in the treatment of scarlet fever, mumps, erysipelas, whooping cough and infections with hemolytic streptococci.

Circulatory Failure in Infectious Disease.—A brief but valuable discussion of the rational treatment of circulatory failure in infections is given by Eggleston.[184] He points out the ineffectiveness of most of the drugs used in the hope of stimulating the heart and outlines the procedure most likely to be beneficial.

Crystalline Virus.—Stanley [185] presented more evidence before the American Association for the Advancement of Science to support the view that the crystalline substance previously reported on was the actual cause of tobacco mosaic disease and not merely carried over with minute amounts of still unrecognized virus. With the newly developed technic of ultracentrifugation at tremendous speed and the knowledge that the crystalline protein previously isolated was of high molecular weight, studies were made of other plant diseases presumably of "virus" origin. As a result a new crystalline protein was isolated from tobacco plants

182. Mudd, S.; Flosdorf, E. W.; Eagle, H.; Stokes, J., and McGuinness, A. C.: The Preservation and Concentration of Human Serum for Clinical Use, J. A. M. A. **107**:956-959 (Sept. 19) 1936.

183. McGuinness, A. C.; Stokes, J., and Mudd, S.: The Clinical Uses of Human Serums Preserved by the Lyophile Process, J. Clin. Investigation **16**:185-196 (March) 1937.

184. Eggleston, C.: Drugs Used in the Treatment of Circulatory Failure in Acute Infectious Diseases, J. A. M. A. **107**:1213-1215 (Oct. 10) 1936.

185. Stanley, W. M., and Wykoff, R. W. G.: The Isolation of Tobacco Ring Spot and Other Virus Proteins by Ultracentrifugation, Science **85**:181-183 (Feb. 12) 1937.

with ring spot disease which differed from the virus of mosaic disease. By similar methods there were isolated a number of other less stable plant viruses which in respect to concentration in the host and to instability were more like certain animal viruses than the abundant and easily manipulated mosaic virus.

Relation of Cancer to Virus Diseases.—Investigators are confronted with a question of great importance as to whether viruses actually cause cancer or whether, like other substances, such as coal tar, they simply provoke some perversion of the internal chemistry of cells which results in cancer. The subject is adequately reviewed by Rous [186] in a Harvey Lecture and needs no further comment here except for brief reference to subsequent contributions.

Murphy [187] is opposed to the view that viruses cause cancer. The only proved relationship, he believes, is that a virus may initiate changes leading to a malignant process, and it has no part in the formal genesis of neoplasms.

Most fowl tumors, except certain ones induced chemically, are transmissible by cell-free filtrates. Those transferable only by grafts of living tumor cells more closely resemble mammalian tumors in this respect. Claude [188] believes that the difficulty of establishing transferred growth in certain cases was due to the presence of some inhibiting factor rather than to the absence of the agent. He found, for instance, that an inhibiting agent could be separated from the tumor-inducing filtrate of a certain chicken tumor by high speed centrifugation, and he applied this method to fowl fibrosarcoma. Tumors developed when the sediment alone was injected into chickens but not if the unspun filtrate was used. He then mixed some of the sediment with its own supernatant fluid and thereby again made the filtrate inert. This indicates that the tumor-forming agent is active only when separated from the neutralizing element. Repetitions of these experiments have thus far failed to show similar results with mammalian tumors. Other investigators have gathered evidence to weaken the theory of the relationship of filtrable viruses to tumor formation. Jobling and Sproul [189] report their studies in which distinct differences were noted between the active agent of the Rous chicken sarcoma and two diseases of virus origin, namely, vaccinia and tobacco mosaic disease. In experiments

186. Rous, P.: The Virus Tumors and the Tumor Problem, Am. J. Cancer **28**:233-272 (Oct.) 1936.

187. Murphy, J. B.: Relation of Filtrable Viruses to Malignant Disease, Proc. Staff Meet., Mayo Clin. **11**:789-790 (Dec. 9) 1936.

188. Claude, A.: Preparation of an Active Agent from Inactive Tumor Extracts, Science **85**:294-295 (March 19) 1937.

189. Jobling, J. W., and Sproul, E. E.: Relation of Certain Viruses to the Active Agent of the Rous Chicken Sarcoma, Science **85**:270-271 (March 12) 1937.

involving the use of both protein and lipid fractions of extracts causing these three diseases the authors were able to produce sarcoma with the lipid extract only. The inability to produce disease with the lipid extract of the known viruses indicates that they are of a different chemical nature. The authors believe that the agent causing chicken sarcoma is not a virus but a product of abnormal cell metabolism, which when injected into normal animals may stimulate normal cells to make a similar substance and thus perpetuate the disease. It is of interest to note how closely this theory resembles the facts associated with the transformation of types of pneumococci, in which any of the nonspecific S forms of pneumococci may be transformed into various specific M types by incubating the S forms together with the heat-killed M forms of the desired type. The question seems to involve the fascinating problem of the transformation of biologic types involving filtrable viruses, bacteria and tissue cells.

Transformation of Biologic Types.—A feature characteristic of scientific development is the theoretical discussion of a subject for years which seems to culminate suddenly in the publication of a number of papers confirming the theory. This has taken place in regard to the transformation of biologic types. The probable mutation of smallpox virus to vaccinia virus and of "street" virus to "fixed" virus of rabies has long been suspected. One may recall experiments with tissue cultures in which monocytes changed into fibroblasts. Numerous observers have suggested that mutation may play a rôle in the changing of types of gonococci or meningococci and among the colon-typhoid group of bacilli. The artificial induction of a change of type specificity among pneumococci is well known. More recently Mooser has caused one variety of typhus organisms to change into another. Andrewes and Smith [190] noted a sudden increase in the virulence of influenza virus in the course of passage through mice. The change is ascribed to the appearance of a mutant form, which thereafter gradually replaced the original form. Andrewes,[191] working with a virus of rabbit fibroma isolated by Shope, found that the virus in his hands no longer produced tumor-like growths when injected into rabbits but gave rise to acute inflammatory lesions. Evidence is presented that the original tumor-forming strain and the inflammatory strain produced cross-immunization and that one was not a contamination or separate strain but apparently a mutant form of the other.

190. Andrewes, C. H., and Smith, W.: Influenza: Further Experiments on the Active Immunization of Mice, Brit. J. Exper. Path. **18**:43-55 (Feb.) 1937.

191. Andrewes, C. H., and Shope, R. E.: A Change in Rabbit Fibroma Virus Suggesting Mutation, J. Exper. Med. **63**:179-184 (Feb.) 1936.

Recently more evidence has been published [192] recording one of the first proved observations on the spontaneous transformation of bacterial types in vivo and in vitro. A strain of Micrococcus tetragenus isolated from the blood of a patient was observed over a period of three years under various adverse circumstances of growth. Four different type-specific strains were derived from the original white variety obtained from the patient. The five types were characterized by distinct and constant biologic characteristics involving the production of pigment and serologic specificity. From each of the types, culture phases of the mucoid, smooth and rough forms were derived. One type was observed to change into another in the animal body and on culture mediums. In another study [193] I attempted to determine the significance of this biologic change of type. The several types were grown under various conditions unfavorable to the growth and life of the organism. Under certain conditions of acidity and heat one group of variants survived, while the second group survived a degree of alkalinity and cold which prevented growth of the other. It appeared that type variation permitted the existence of a strain of bacteria under a wide range of environmental conditions. I believe that evidence of selection, as just described, might explain to some extent what is meant by "virulence." For instance, a variant form of a given organism which finds conditions in the animal body suitable for its growth might be regarded as "virulent." Spontaneous type transformation or mutation may help to explain obscure questions of the origin of certain infectious diseases or of epidemics.

An unsolved problem of great importance involves the forces which cause type transformation or mutation. Chemical changes are believed to be responsible. The subject was discussed by S. P. Reimann [194] at the Wisconsin Cancer Conference as follows:

> Mutation has been observed in all species of plants and animals in which a sufficient number of individuals have been observed. In undifferentiated cells there are present many more chemical compounds with open bonds than are present in differentiated cells. These open bonds have innumerable possibilities of chemical combination. It is known that the potency of any undifferentiated cell is more than its realization. Which of its numerous potencies it displays depends upon the environment. In terms of chemistry, which of the open bonds and with what groups they are combined depends upon the chemical molecules, atoms, ions, or radicles offered by the environment, all of course, subject to the guidance of the inherited species specificity.

192. Reimann, H. A.: Bacterial Type Transformation, Proc. Soc. Exper. Biol. & Med. **35**:64-65 (Oct.) 1936; Bacterial Type Transformation: IV. Micrococcus Tetragenus Infection, J. Bact. **33**:499-511 (May) 1937.

193. Reimann, H. A.: The Significance of Bacterial Variation: V. Micrococcus Tetragenus Infection, J. Bact. **33**:513-523 (May) 1937.

194. Reimann, S. P.: The Biology of the Cancer Cell, Proc. Wisconsin Cancer Conf., to be published, 1937.